

Pathobiology of Airway Remodeling in Asthma: The Emerging Role of Integrins

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Abstract: Airway remodeling is a complex clinical feature of asthma that involves long-term disruption and modification of airway architecture, which contributes significantly to airway hyperresponsiveness (AHR) and lung function decline. It is characterized by thickening of the airway smooth muscle layer, deposition of a matrix below the airway epithelium, resulting in subepithelial fibrosis, changes within the airway epithelium, leading to disruption of the barrier, and excessive mucous production and angiogenesis within the airway wall. Airway remodeling contributes to stiffer and less compliant airways in asthma and leads to persistent, irreversible airflow obstruction. Current asthma treatments aim to reduce airway inflammation and exacerbations but none are targeted towards airway remodeling. Inhibiting the development of airway remodeling or reversing established remodeling has the potential to dramatically improve symptoms and disease burden in asthmatic patients. Integrins are a family of transmembrane heterodimeric proteins that serve as the primary receptors for extracellular matrix (ECM) components, mediating cell–cell and cell–ECM interactions to initiate intracellular signaling cascades. Cells present within the lungs, including structural and inflammatory cells, express a wide and varying range of integrin heterodimer combinations and permutations. Integrins are emerging as an important regulator of inflammation, repair, remodeling, and fibrosis in the lung, particularly in chronic lung diseases such as asthma. Here, we provide a comprehensive summary of the current state of knowledge on integrins in the asthmatic airway and how these integrins promote the remodeling process, and emphasize their potential involvement in airway disease.

Keywords: asthma, airway remodeling, integrins, matrix, fibrosis, biomechanics

Introduction

Asthma is a heterogeneous chronic inflammatory disease of the airways characterized by airway hyper-responsiveness, bronchoconstriction, and airway remodeling. Asthma affects over 260 million people worldwide and was responsible for over 21 million Disability-adjusted Life Years (DALYs) in 2019,¹ representing significant morbidity and economic burden. The prevalence of asthma is highest in countries with the highest socio-demographic index (SDI); however, death rates are highest in countries with low–middle SDI.¹

The symptoms of asthma include wheezing, shortness of breath, chest tightness, and cough that fluctuate in frequency and intensity, as well as variable expiratory airflow restriction.² Treatment includes targeting bronchoconstriction through the use of β_2 adrenergic agonists, or some cases muscarinic receptor antagonists, and reducing airway inflammation via inhaled or oral corticosteroids. Such an approach is sufficient to control symptoms in most patients, however, some patients suffer from difficult-to-treat asthma, with uncontrolled symptoms despite good adherence to treatment. Severe asthma, defined as uncontrolled symptoms despite treatment with highest doses of inhaled corticosteroids in combination with an additional controller medication (eg, long-acting β_2 agonist), affects approximately 5–10% of patients and is associated with frequent and uncontrolled exacerbations, and a long-term decrease in lung function.^{3–5}

Remodeling of the airways contributes to airway wall thickening and has a detrimental effect on asthma. It is associated with accelerated decline in lung function, an increased rate of exacerbation in asthmatic patients, and

irreversible airflow obstruction.^{6–8} Thickening of the airways is not limited to patients suffering from the severest forms of the disease and can be evident even in mild forms of asthma; however, the degree of thickening is associated with increased disease severity and degree of airflow obstruction.^{9,10} Airway remodeling is thought to play a vital role in the uncontrolled symptoms and disease burden observed in severe asthmatics. Over recent years many studies have implicated a family of cell surface receptors known as integrins in the development and progression of airway remodeling. This review aims to bring together our current knowledge of how integrins may either drive or inhibit airway remodeling in asthma, and discuss the potential utility of targeting integrins as a therapeutic strategy in severe asthma.

Airway Remodeling in Asthma

Airway remodeling is the collective term given to the structural changes that occur within the asthmatic airway. These changes include sub-epithelial fibrosis, thickening of the airway smooth muscle (ASM) layer, mucous gland hyperplasia, angiogenesis, and loss of epithelial layer integrity, all of which contribute to a thickened and stiffened airway wall. The development of airway remodeling begins early in the disease course, with structural changes being evident in preschool children with clinically confirmed wheeze, even prior to an asthma diagnosis.^{11–13}

The underlying mechanisms driving the development of airway remodeling are largely unclear and likely to be extremely complex and multifaceted. While for many years airway remodeling was thought to result from the presence of chronic inflammation within the asthmatic airway, this has more recently been questioned. Structural changes in the airways of preschool wheezers do not correlate with inflammatory cell counts in bronchoalveolar lavage fluid.¹¹ It is possible that different features of airway remodeling differ in the underlying mechanisms driving them. The following section will discuss the potential mechanisms responsible for the development and progression of airway remodeling in asthma.

Potential Mechanisms Driving Airway Remodeling

Airway inflammation has long been thought to drive the development of asthmatic airway remodeling. Asthma is largely driven by T_{H2} inflammation associated with interleukin-4 (IL4), interleukin-5 (IL5), and interleukin-13 (IL13), and T_{H2} inflammation remains a crucial target in asthma therapy development. However, a cluster analysis of asthmatic patients has suggested that patients with fixed airflow obstruction and evident airway remodeling have predominantly T_{H17} rather than T_{H2} driven inflammation.¹⁴

Further evidence of a link between inflammation and airway remodeling comes from *in vivo* and *in silico* models of asthma. A theoretical model of airway remodeling demonstrates that inflammation is sufficient to promote thickening of the airway wall towards the lumen, although increased thickening occurs when biomechanical contractile forces and inflammation are modeled simultaneously,¹⁵ suggesting interplay of multiple pathways. Additionally, numerous mouse models have highlighted a potential link between inflammation and remodeling. For example, Interleukin-33 (IL33) can exacerbate allergen-induced inflammation and remodeling in a mouse model,¹⁶ and M₂ macrophages, which IL33 promotes polarization towards,^{17,18} has been associated with allergen-induced remodeling in mice.¹⁹

From the studies described above it is clear that the mechanistic link between airway inflammation and airway remodeling is still ambiguous. The fact that remodeling occurs very early in the disease course, including in young children with wheeze prior to a diagnosis of asthma,^{11–13} suggests that chronic inflammation may not be the sole driver of airway remodeling.

An alternative possibility is that the mechanical environment of the asthmatic airway drives remodeling changes. This was initially suggested in 2011 when Grainge et al²⁰ demonstrated remodeling changes in response to bronchoconstriction in the absence of additional inflammation. Mechanistically, contraction of ASM cells and airways causes activation of the pro-remodeling cytokine TGF β and downstream remodeling changes.^{21–23} Moreover, pharmacological inhibition of transient receptor potential vanilloid-1 (TRPV1), which can modulate ASM tone, reduces airway remodeling *in vivo*.^{24,25} Mathematical modeling has also suggested that airway contraction contributes to remodeling.¹⁵

In addition to contractile mechanical forces promoting airway remodeling it is also possible that non-contractile biomechanical forces contribute.²⁶ ECM proteins within the asthmatic airway wall can promote proliferation of ASM cells²⁷ and drive remodeling changes in vivo.²⁸ Additionally, altered mechanics due to a stiffer airway wall may drive remodeling changes. Increased matrix stiffness promotes epithelial–mesenchymal transition,²⁹ collagen production by fibroblasts,³⁰ and ASM cell proliferation,³¹ all of which may contribute to airway remodelling. Recently, a link between matrix crosslinking, which stiffens ECM, and the development of asthmatic airway remodeling has been described whereby the matrix crosslinking enzyme lysyl oxidase-like-2 (LOXL2) has been implicated.³² Crucially, LOXL2 levels were increased in asthmatic ASM cells and pharmacological inhibition of LOXL2 in vivo reduced allergen-induced airway remodeling.³²

Integrins

Integrins are heterodimeric transmembrane receptors that facilitate cell–cell and cell–matrix interactions. They provide a direct link between the environment outside of the cell and the cytoskeleton within the cell, and involved in the transmission of biomechanical signals. The family is composed of 24 mammalian members, made up by a variety of combinations of alpha (α) and a beta (β) subunit; there are eight distinct β subunits and 18 distinct α subunits.³³ The α subunit is responsible for the ligand binding properties of integrins, while the downstream intracellular signaling events are co-ordinated by the β subunit. Some integrins can bind to only one type of ligand, while other integrins are able to recognize several ECM proteins.

Integrins can mediate bi-directional signals through the cell membrane; inside-out signalling regulates extracellular binding activity of integrins and thereby switching into active conformation. On the other hand, binding of ECM proteins on integrins activate signals that are transmitted into the cells known as outside-in signaling.³³ These signaling events modulate roles in cell attachment, survival, proliferation, leukocyte trafficking, cell differentiation, cytoskeleton organization, cell migration, gene expression, tumorigenicity, and intracellular pH.

Integrins combine with multiple proteins to form integrin adhesion complexes (IAC), also known as the integrin adhesome, to activate downstream signaling pathways. To date the literature suggests such complexes involve at least 232 distinct integrin-associated proteins (IAP),³⁴ including talin, paxillin, kindlins, filamin, vinculin, integrin-linked kinase (ILK), focal adhesion kinase (FAK), Src family protein tyrosine kinases (SFK), and GTPases of the Rho family. Such complexes can be split into four compartments: the ECM, the integrin, IAPs, and the actin cytoskeleton.³⁴ The wide-ranging and diverse functions of just 24 distinct integrins are largely dependent on the complexity and diversity of IACs.

Several integrins are expressed within the lung and have roles in lung development, including branching morphogenesis, epithelial cell polarization, and differentiation.^{35,36} Expression of integrins varies across lung cell types and at varying times of development. Within the airway epithelium eight integrins are expressed, namely $\alpha 2\beta 1$, $\alpha 3\beta 1$, $\alpha 5\beta 1$, $\alpha 6\beta 4$, $\alpha 9\beta 1$, $\alpha \nu\beta 5$, $\alpha \nu\beta 6$, and $\alpha \nu\beta 8$.^{36–38} In some cases, integrin subunit expression in the epithelium is dramatically increased during inflammation or repair, most notably for the epithelially-restricted integrin $\alpha \nu\beta 6$.^{37,39–41} Within the lung mesenchymal cells expression of $\alpha 5\beta 1$, $\alpha \nu\beta 3$, $\alpha 2\beta 1$, $\alpha 4\beta 1$, $\alpha 5\beta 1$, $\alpha \nu\beta 5$, and $\alpha 7\beta 5$ have all been reported.^{22,42,43} Lung inflammatory cells also express integrin receptors; macrophages express $\beta 2$ integrins, $\alpha 4\beta 1$ and $\alpha 5\beta 1$,^{44,45} and T lymphocytes are known to express $\alpha 4\beta 1$, $\alpha 5\beta 1$, $\alpha E\beta 7$ and $\beta 2$ integrins.⁴² Eosinophils, which have an important role in the pathophysiology of asthma, have a distinctive combination of eight integrins, $\alpha 4\beta 1$, $\alpha 6\beta 1$, $\alpha L\beta 2$, $\alpha D\beta 2$, $\alpha M\beta 2$, $\alpha X\beta 2$, and $\alpha 4\beta 7$.^{46,47}

The known function of integrins and integrin adhesomes make them attractive candidates for understanding how mechanical cues, including contractile forces and matrix stiffening, might influence airway remodeling processes. Furthermore, integrins are well-known for regulating leukocyte and inflammatory cell trafficking, which could also have important implications for asthma development and progression and for airway remodeling. The following section will discuss the role of integrin superfamily members in mediating specific airway remodeling processes in a variety of lung cells important to asthma pathogenesis. We have summarised how specific integrin heterodimers might be involved in asthmatic airway remodeling process in [Table 1](#) and [Figure 1](#).

Table 1 Overview of Integrins Involved in Asthmatic Airway Remodeling

	Integrins	Role	Reference
Airway hyper-responsiveness and ASM thickening	$\alpha 5\beta 1$ $\alpha 2\beta 1$	Inhibits IL-13-induced contraction ASM	[85,86]
	$\alpha v\beta 5$	Contraction-induced activation of TGF β in ASM cells	[22]
	$\alpha 8\beta 1$ $\alpha 9\beta 1$	Negative regulation of ASM contraction	[93,94]
	$\alpha 2\beta 1$, $\alpha 4\beta 1$ and $\alpha 5\beta 1$ $\beta 1$	Regulates ASM proliferative responses	[31,98,99]
	$\alpha 7\beta 1$	Promotion of ASM survival and differentiation	[100]
Epithelial changes	$\beta 4$	Epithelial cell senescence	[60]
	$\beta 1$	Mucous production	[68,69]
	$\beta 3$	Protects against goblet cell hyperplasia	[70]
Subepithelial fibrosis	$\alpha 5\beta 1$	Fibronectin deposition by ASM cells	[104]
	$\alpha v\beta 8$	Airway fibrosis TGF β activation	[117,179]
	RGD-binding	ECM gene expression in ASM	[125]
Angiogenesis	$\alpha v\beta 3$, $\alpha v\beta 5$	Angiogenesis	[139,141]
	$\alpha 1$, $\alpha 2$ subunits	VEGF-induced angiogenesis	[180]

Epithelial Changes in Airway Remodeling

The epithelial layer serves as a physical barrier to the exterior environment. As a result, it is the lungs' first line of defence against foreign bodies inhaled during breathing. In addition, the healthy airway epithelium modulates immune responses and promotes the expulsion of inhaled particles through mucous production and cilia movement. The asthmatic airway epithelium undergoes dramatic phenotypic changes resulting in loss of epithelial integrity through epithelial shedding and increased mucous production via mucous gland hyperplasia.

Loss of airway epithelium is a well-documented phenomenon in asthma^{48–51} and is linked with airway hyper-reactivity.^{48,50} Loss of epithelial integrity occurs early in the disease course,⁴⁹ and is thought to result from cellular apoptosis, senescence, and ineffective repair mechanisms.^{52,53} The asthmatic airway epithelium expresses markers of cellular injury/repair including increased epidermal growth factor receptor (EGFR),^{54,55} transforming growth factor β (TGF β),^{56,57} and decreased E-cadherin.⁵⁸ Furthermore, apoptosis and proliferative pathways are altered.⁵⁹

Senescence of the epithelium occurs in asthma⁵³ and may promote asthma development by compromising epithelial integrity and barrier function. Moreover, epithelial cell senescence drives thymic stromal lymphopietin (TSLP)-induced airway remodeling.⁵³ Crucially, airway epithelial senescence can be driven by a deficiency in integrin $\beta 4$ expression in a P53 dependent manner,⁶⁰ and the asthmatic human bronchial airway epithelium has reduced integrin $\beta 4$ expression.⁶¹ In the ovalbumin mouse model of asthma, integrin $\beta 4$ expression is reduced on the airway epithelium and is associated with structural disruption of the epithelial layer.⁶² Together, these studies in human asthmatic patients and animal models of asthma suggest a crucial role for $\beta 4$ integrins in maintaining epithelial integrity in the airway.

In addition to loss of epithelial integrity, the asthmatic airway produces excessive quantities of mucous. MUC5AC and MUC5B are polymeric mucins that are significantly increased in the asthmatic airway and MUC5AC levels correlate with clinical measures of asthma including fractional exhaled nitric oxide (FeNO), sputum eosinophils, and airway hyper-responsiveness.⁶³ A key driver of increased mucous production is goblet cell hyperplasia, which is evident in mild

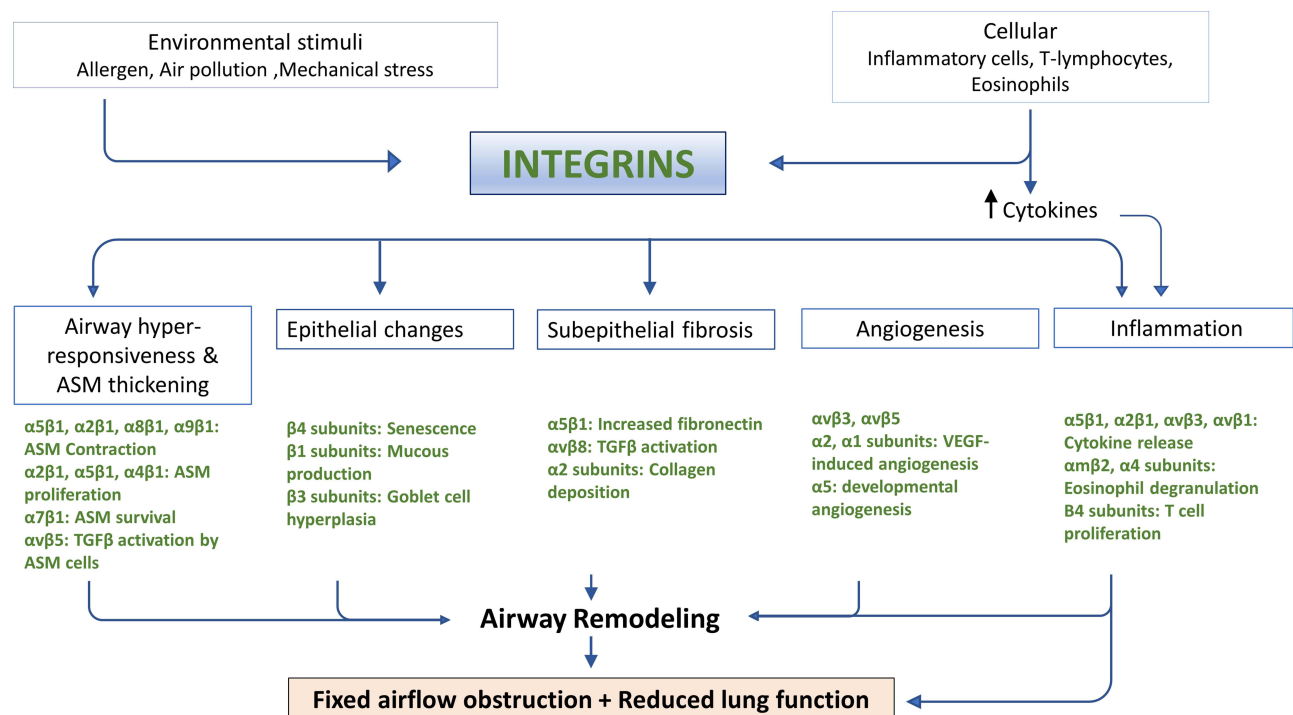


Figure 1 Schematic diagram giving an overview of how different integrin heterodimers expressed by a variety of lung cell types may contribute to the development and/or progression of airway remodeling in asthma. Both environmental and cellular stimuli converge upon integrin signaling pathways in a variety of cell types to contribute to airway hyper-responsiveness and ASM thickening, mucous over-production, subepithelial fibrosis, new blood vessel formation, and airway inflammation.

through to severe asthma.^{64,65} Additionally, mucous over-production can be driven by paracrine interactions with underlying airway smooth muscle cells.⁶⁶ Overall, mucous gland hyperplasia and excessive mucus production can lead to mucous plugging of the airway, reduced airway lumen area, and airflow obstruction.⁶⁷ Integrins have been implicated in mucous overproduction and goblet cell hyperplasia. $\beta 1$ integrins have recently been shown to regulate cellular and secreted MUC5AC and MUC5B production in lung epithelial cells.^{68,69} Conversely, interactions between Mfge8 and integrin $\beta 3$ subunits protect against allergen induced airway remodeling changes, including goblet cell hyperplasia.⁷⁰

Increased Airway Smooth Muscle Mass (ASM)

Thickening of the airway smooth muscle (ASM) layer is a common and prominent feature of asthmatic airway remodeling. In the healthy airway, ASM cells are thought to play an important role in modulating respiratory airway tone. During disease processes, however, they have an important role in inflammatory and remodeling processes, releasing chemokines, pro-inflammatory and/or pro-fibrotic cytokines, and ECM proteins,^{22,26,71–73} which contributes to asthma pathogenesis.

In the asthmatic airway increased ASM mass appears to be driven by both increased myocyte size (hypertrophy) and increased myocyte number (hyperplasia), which are in turn associated with disease duration and severity.⁷⁴ Some studies have suggested that the increase is due to hyperplasia rather than hypertrophy⁷⁵ and others have suggested that hyperplasia only occurs in cases of fatal asthma.⁷⁶ The causes of increased ASM mass in asthma are likely to be multifaceted. Interactions between ASM cells and airway epithelial cells can promote increased ASM cell proliferation and production of inflammatory cytokines and chemokines,⁷⁷ suggesting a role for paracrine signaling between the two cell types. Furthermore, interactions between ASM cells and $CD4^+$ T lymphocytes, known to be crucial to the pathogenesis of asthma, can increase ASM cell proliferation.⁷⁸ Numerous ASM cell mitogens have been implicated in asthma, including Platelet derived growth factor (PDGF),⁷⁹ TGF β ⁸⁰ epidermal growth factor (EGF),⁷⁸ heparin-binding EGF,⁸¹ and vascular endothelial growth factor (VEGF).⁸² In certain cases, such as PDGF,⁸³ these mitogens can also

promote ASM cell migration, which may contribute to the thickening of the ASM layer and expansion of the airway wall. Regardless of the underlying mechanism, during an asthma exacerbation, the thickened ASM bundle contributes to the airway-constricting capacity of the muscle⁸⁴ and is thought to contribute to fixed airflow obstruction in severe asthma.

Several integrins have been linked with the contractile function of ASM cells. The fibronectin binding $\alpha 5\beta 1$ integrins are involved in ASM cell contraction; functional blockade of $\alpha 5\beta 1$ interrupts the function of focal adhesions, reduces interleukin-13 (IL13)-induced contraction of tracheal rings and inhibits airway hyper-responsiveness in vivo.⁸⁵ Crucially, pharmacological inhibition of $\alpha 5\beta 1$ had no effect on baseline tone of the smooth muscle rings and only reduced contraction in response to asthma-relevant contractile agonists, making it a potentially attractive approach for therapeutic targeting in asthma as the homeostatic functions of ASM could be preserved.⁸⁵ A similar role has recently been identified for $\alpha 2\beta 1$ integrins in regulating IL13-induced contraction, in this case through interrupting ASM cell tethering to collagen I and laminin-111.⁸⁶

Contraction of ASM cells occurs via force transmission through polymerization and reorganization of the actin cytoskeleton. The cytoplasmic tail of β integrins binds to actin filaments through “linker” proteins such as vinculin, talin, and α -actinin, whereas the extracellular component of integrins interacts with the extracellular matrix to tether the cell.⁸⁷ Force transmission between the cell and the extracellular matrix is therefore delivered by the actin–integrin–matrix complex. Actin filament polymerization and myosin activation are two concurrent biochemical mechanisms that are critical for smooth muscle contraction homeostasis, however, inhibiting actin polymerization limits smooth muscle force generation with minimal impact on myosin light chain phosphorylation.^{88–90} Crucially, actin-regulatory proteins are involved in regulating proliferation of smooth muscle cells,⁹¹ demonstrating how force transmission through integrins may influence cell proliferation and remodeling. Finally, TGF β , which can be activated by ASM cells via integrins in response to reorganization of the actin cytoskeleton,²² augments ASM cell contraction in a RhoA-independent manner.⁹² This suggests a perpetual feedback loop whereby bronchoconstriction causes integrin-mediated TGF β activation to promote airway remodeling, which in turn increases the contractility of the ASM cells and contributes to fixed airflow obstruction by increasing the baseline tone of the ASM layer.

In addition to promoting cell contractility through interactions with actin, integrin superfamily members are also involved in negative regulation of ASM contraction. Ligation of $\alpha 8\beta 1$ integrins on ASM cells by milk fat globule-EGF factor-8 (Mfge8) proteins prevents IL13-induced ASM contraction.⁹³ $\alpha 9\beta 1$ integrins are also capable of negatively regulating ASM contraction. Loss of, or inhibition of, $\alpha 9\beta 1$ integrins in mice increases airway contraction.⁹⁴ These studies all highlight the importance of ASM cell interactions with matrix proteins through cell surface integrins to regulate ASM contraction and airway narrowing. As discussed previously, uncontrolled bronchoconstriction can promote airway remodeling via integrin-mediated activation of the pro-remodeling cytokine TGF β .^{21–23} Taken together, it is clear that integrins have a potentially crucial role in regulating both pathological ASM contraction and downstream pro-remodeling effects, representing a direct link between uncontrolled asthma symptoms and the development of airway remodeling through a mechanobiological mechanism.

In addition to effects on ASM contraction, integrins expressed by ASM cells may also promote migration and proliferation of ASM cells, which is thought to contribute to thickening of the ASM layer and airway lumen narrowing in airway remodeling.⁹⁵ Global blockade of RGD-binding integrins with a synthetic RGDS peptide attenuates allergen-induced ASM hyperplasia and hypercontractility, suggesting a crucial role for this subset of integrins in ASM remodeling.⁹⁶ $\beta 1$ integrins are highly expressed in ASM cells plus other mesenchymal cells in the lung, including myofibroblasts, and have recently been shown to localize key adaptor proteins at the leading edge of migrating ASM cells.⁹⁷ Additionally, $\beta 1$ integrins have been implicated in pro-proliferative responses of ASM cells to increasing matrix stiffness.³¹ $\alpha 2\beta 1$, $\alpha 4\beta 1$, and $\alpha 5\beta 1$ have all been shown to regulate ASM cell proliferation.⁹⁸ The matrix protein fibulin-5 has been implicated in this process through binding to $\beta 1$ integrins to promote ASM cell proliferation via the mechanosensing YAP/TAZ pathway.⁹⁹ Furthermore, laminin binding to $\alpha 7\beta 1$ integrins promotes ASM cell survival and differentiation to a contractile phenotype.¹⁰⁰ All together these studies support an important role of $\beta 1$ integrins in regulating increased ASM mass in asthmatic airway remodeling.

Subepithelial Fibrosis

Subepithelial fibrosis in the asthmatic airway occurs in the lamina reticularis, just below the basement membrane, where ECM proteins such as interstitial collagens, fibronectin, tenascin, and proteoglycan accumulate.¹⁰¹ Subepithelial fibrosis is linked to asthma severity; collagen expression in the airway wall is higher in patients with moderate or severe asthma compared with those with mild disease,⁵⁷ and the degree of subepithelial fibrosis is inversely correlated with FEV1.¹⁰² Increased deposition and decreased degradation of extracellular matrix (ECM) proteins is one of the major hallmarks of fibrosis regardless of organ or tissue type, and is primarily controlled by fibroblasts and myofibroblasts. Within the asthmatic airway, the number of myofibroblasts present correlates with the amount of collagens and tenascin detected in the subepithelial region.¹⁰² Furthermore, fibrocytes, which can differentiate into myofibroblasts, are increased in asthma and may contribute to subepithelial fibrosis.¹⁰³

Information relating to a direct role for integrins in regulating matrix deposition in asthma is limited. In vitro studies have shown that treatment of ASM cells with the pro-remodeling cytokine TGF β leads to increased fibronectin deposition via an $\alpha 5\beta 1$ mediated mechanism involving ERK signaling.¹⁰⁴ Additionally, in murine models it has been reported that interleukin-32 (IL32) reduces allergen-induced fibrosis via suppression of the integrin-FAK-paxillin signaling axis.¹⁰⁵

Transforming growth factor- β (TGF β) is thought to be a key driver of subepithelial fibrosis in asthma. *TGFBI* mRNA is increased in bronchial biopsies from asthmatic individuals and levels correlate with the degree of subepithelial fibrosis.¹⁰⁶ Furthermore, all three isoforms of TGF β are increased in the asthmatic airway.^{56,57,107–109} TGF β causes transdifferentiation of airway fibroblasts into highly synthetic, matrix producing myofibroblasts^{110,111} and increases production of matrix proteins by fibroblasts/myofibroblasts.^{112,113} Crucial evidence from murine animal models shows that inhibition of both TGF $\beta 1$ and 2 with isoform-specific function blocking antibodies reduced allergen-induced subepithelial collagen deposition,¹¹⁴ and intra-tracheal instillation of TGF $\beta 1$ is sufficient to cause subepithelial fibrosis.¹¹⁵ Finally, there is recent evidence suggesting that human bronchial fibroblast responses to TGF β are altered in asthma, with pro-fibrotic responses being increased while anti-fibrotic responses are decreased.¹¹⁶ Together, these studies highlight a crucial role for TGF β in regulating subepithelial fibrosis in asthma.

$\alpha v\beta 8$ integrins are capable of activating TGF β via recruitment of matrix metalloproteinases, which proteolytically cleave the latent TGF β complex on the cell surface.¹¹⁷ Proteolytic cleavage of TGF β has been previously reported,^{71,118} however, $\alpha v\beta 8$ is the only integrin described thus far that mediates TGF β activation via proteolysis. Importantly, expression of $\alpha v\beta 8$ integrins is increased in asthma¹¹⁹ and expression of MMP-9 and MMP-8 in the airway inversely correlate with FEV1.^{120,121} Other cell types are capable of activating TGF β via integrins including myofibroblasts, lung epithelial cells, and ASM cells.^{22,122–124} This raises the possibility that integrin-mediated TGF β contributes to matrix deposition in the asthmatic airway, although this remains to be definitively proved.

Integrins have been implicated in inflammatory cell-mediated mechanisms of airway remodeling. Inhibiting RGD-binding integrins peptide on eosinophils using an RGDS blocks their ability to bind to ASM cells and interrupts the eosinophil-induced increased in ECM gene expression.^{125,126} Despite these studies it has been shown that a blockade of RGD-binding integrins, again using a synthetic RGDS peptide, reduces markers of ASM remodeling in vivo but has no effect on airway fibrosis, suggesting that this subset of integrins does not mediate subepithelial fibrosis.⁹⁶ Finally a limited study has shown that collagen deposition in the asthmatic airway is inversely correlated with expression of $\alpha 2$ subunits on blood and CD4⁺ cells.

Angiogenesis

Angiogenesis refers to the process of forming new blood vessels. Increased vascularity of the asthmatic airway is a common observation and is evident in newly diagnosed asthma patients.^{127–129} The implications of increased vascularity on the pathogenesis of asthma and airway remodeling are still somewhat unclear. Correlations between increased vascularity and decreased lung function in asthma are inconsistent, with some reports finding a correlation¹²⁸ and others reporting no link.¹²⁷ Furthermore, animal models have shown that reducing angiogenesis experimentally using the inhibitor of angiogenesis, tumstatin, does not improve lung function.¹³⁰ Although a link between increased

vascularity and decreased lung function in asthma is still unclear, angiogenesis within the asthmatic airway wall enhances inflammatory cell recruitment and can cause edema, which may contribute to asthma pathogenesis.¹²⁹

VEGF is one of the most potent activators of endothelial cell growth and promotes vascular permeability. VEGF levels in bronchial biopsies, serum, and bronchoalveolar lavage fluid are increased in asthma,^{131–133} and VEGF expression within airway cells correlates with the number of vessels.¹³⁴ ASM cells isolated from asthmatics can drive angiogenesis via increased VEGF secretion.¹³⁵ Crucially, pharmacological inhibition of VEGF signaling has shown promise in experimental models of asthma by reducing expression of growth factors, improving epithelial barrier function,^{136,137} and reducing markers of airway remodeling.¹³⁸

Integrins have long been implicated in angiogenic processes, with the earliest descriptions demonstrating links between $\alpha\beta3$ and $\alpha\beta5$ and angiogenesis.^{139,140} Single nucleotide polymorphisms (SNPs) within the *ITGB3* gene are associated with asthma pathogenesis.¹⁴¹ Additionally, pharmacological inhibition of $\alpha\beta3$ prevents blood vessel maturation.¹⁴² However, genetic knockout of either $\beta3$ or $\beta5$ subunits does not alter vascular development.^{143,144}

Genetic knockdown of integrin subunits has highlighted some potentially important roles in angiogenesis during development, which may also be important in disease. For example, genetic loss of integrin $\alpha5$, which binds to fibronectin, leads to vascular defects and mice that are embryonic lethal, similar to the fibronectin knockout animals.¹⁴⁵ This suggests a crucial role of $\alpha5$ integrins and fibronectin in early angiogenesis. However a separate study found that inhibiting $\alpha5\beta1$ with a small molecule inhibitor alpha5beta1 Integrin blockade inhibits lymphangiogenesis in airway inflammation and interrupts lymphatic vessel development without affecting blood vessel development.¹⁴⁶ Finally, an important role for endothelial cell $\alpha2\beta1$ integrin in promoting lumen formation in new capillaries has been described.¹⁴⁷

Integrins in Airway Remodeling: Inflammation

Chronic airway inflammation is a hallmark of asthma and, as has been discussed previously in this article, has the potential to influence pro-remodeling pathways. Several integrins including $\alpha2\beta1$, $\alpha5\beta1$, $\alpha\beta3$, and $\alpha\beta1$ have been linked with increased cytokine release when ASM cells are cultured on collagen and fibronectin, suggesting that an altered mechanical environment may influence the inflammatory environment within the airway wall.¹⁴⁸

Eosinophils are thought to be important to the pathogenesis of asthma and they express numerous integrins. Integrins have a key role in mediating migration of eosinophils from the blood into the lung, where they accumulate in asthma.¹⁴⁹ Integrins, particularly $\beta2$ integrins such as $\alpha\beta2$ and $\alpha4$ integrins, have been implicated in eosinophil degranulation and inflammatory mediator release.^{150–152} In addition, $\alpha4$ integrin binding to its ligand fibronectin via Fas antigen signaling increases the eosinophil survival, which may contribute to airway eosinophilia in asthma.¹⁵³

Airway neutrophilia is associated with increased asthma severity and asthma that is refractory to corticosteroids, the backbone of asthma treatment.¹⁵⁴ There is a paucity of research focused directly upon a potential role for integrins in driving airway neutrophilia in asthma; however, integrins, particularly $\beta2$ integrins, are well known to regulate neutrophil recruitment to sites of inflammation.^{155,156} Furthermore, neutrophils and their products have been implicated in lung fibrogenesis in other chronic lung diseases such as interstitial lung disease (ILD). For example $\alpha\beta2$ integrins can regulate neutrophil extracellular trap (NET) formation in ILD,¹⁵⁷ and secretory leukocyte protease inhibitor (SLPI), which inhibits neutrophil elastase, has differential effects on collagen expression in mouse lung tissue.¹⁵⁸ Previous work has shown that integrin expression by sputum neutrophils in asthmatic patients is aberrant compared with healthy controls,¹⁵⁹ however, whether such changes in integrin expression affect the overall activity of neutrophils in asthma and the impact this has on airway remodeling is yet to be elucidated.

Exposure to allergens causes an increase in T_{H2} cell infiltration and T_{H2} cytokine expression in asthmatic patients. T_{H2} cells co-ordinate allergy-induced asthmatic inflammatory responses through Th2 cytokines (IL-4 and IL-5), causing eosinophil infiltration and hyper-responsiveness of the airways.¹⁶⁰ Airway epithelial cells, by acting as antigen presentation cells (APCs), can cause T-cell activation and proliferation, and silencing $\beta4$ integrins in asthmatic airway epithelial cells impairs their antigen presentation capacity and decreases T-cell proliferation.¹⁶¹ This is one possible integrin-dependent mechanism that may contribute to T_{H2} inflammation bias in asthmatic airways.

Therapeutic Targeting of Integrins to Impact Airway Remodeling

To date no drug has been developed that specifically targets the development and progression of airway remodeling. Corticosteroids, which are the mainstay of asthma treatment and primarily target airway inflammation, can reduce several markers of airway remodeling, including ASM proliferation,¹⁶² TGF β expression in fibroblasts,¹⁶³ and VEGF expression by epithelial cells,¹⁶⁴ and can reconstitute epithelial structure.¹⁶⁵ Despite these effects, airway remodeling persists in asthmatic patients despite long-term treatment with inhaled or oral corticosteroids, suggesting there is no overwhelming impact of corticosteroids on airway remodeling in asthmatic patients.

In recent years several new biological therapies have been developed and approved, particularly for the treatment of severe asthma, some of which have shown some effects on airway remodeling. Mepolizumab, a clinically approved anti-IL5 monoclonal antibody, has been shown to reduce airway wall thickness in CT scans¹⁶⁶ and reduce matrix protein deposition in bronchial biopsies.¹⁶⁷ Benralizumab is another monoclonal antibody that targets IL5 signaling, which computational modeling has suggested reduces ASM mass and the number of tissue myofibroblasts present in the airway wall.¹⁶⁸ Omalizumab targets IgE for the treatment of allergic asthma and has been shown to reduce airway wall thickness when measured by computed tomography.¹⁶⁹ Research into the effects of other new monoclonal antibody therapies such as dupilumab (anti-IL4 receptor) and reslizumab (anti-IL5) are yet to be published, however, the former studies suggest that inhibiting T_{H2} inflammation may reduce asthmatic airway remodeling in severe asthma patients. Whether such treatments can sufficiently reduce airway remodeling to lead to long-term positive effects on fixed airflow obstruction or slow the decline in lung function seen in asthmatics, which is thought to be driven by airway remodeling, is likely to be the focus of ongoing studies into the utility of biological therapies. Another key question that remains to be answered is whether therapeutic treatment of airway remodeling will be sufficient or whether prophylactic treatment much earlier in the disease course will be required for the biggest clinical benefit.

Research Dilemmas in Airway Remodeling

As discussed above, airway remodeling is a complex and diverse collection of structural changes involving many tissues and cell types. Despite the introduction of various new therapies for asthma in recent years including various biological treatments targeting airway inflammation, there has yet to be an effective treatment for airway remodeling. This is potentially a result of the many specific challenges associated with researching the underlying mechanisms driving airway remodeling, which were highlighted in detail in an American Thoracic Society statement in 2017,¹⁷⁰ and which will be discussed briefly here.

Lack of Appropriate Animal Models

A major hindrance to research investigating airway remodeling and asthma pathogenesis more widely is the lack of an appropriate animal model. Mice are the most commonly used species for in vivo models of asthma and airway remodeling, however, rats, guinea pigs, and larger species including pigs, sheep, and horses are also used.¹⁷¹

A significant drawback to animal models of asthma is that asthma is a human disease that does not spontaneously occur within the animal kingdom, with the exception of eosinophilic bronchitis in cats and heaves in horses, both of which are obstructive airway diseases with some similarities to asthma. Animal models are therefore largely dependent upon sensitizing animals experimentally to an allergen and then delivering that allergen to the airways to elicit an allergic inflammatory response.¹⁷¹ Such models are advantageous when studying how allergy and/or inflammation drive features of asthma; however, as discussed above, the relative roles of these processes in driving airway remodeling is still largely unclear and so using such models to drive airway remodeling in animals may not accurately reflect the pathogenesis driving remodeling in man.

Size and anatomical differences between human lungs and the species used for models of asthma and airway remodeling also have the potential to negatively impact the utility of findings from such models. For example the human lung has a vastly greater number of branching airways compared with mouse lungs, the effect of which on the development of remodeling is unclear with our insufficient understanding of the mechanisms driving remodeling.¹⁷⁰ Recent methodological advances in assessing airway remodeling in airways of various sizes in murine models of asthma¹⁷² may aid our understanding of the heterogeneous nature of remodeling, albeit within the confines of a rodent disease model discussed above.

Lack of Uniformity in Core Experimental and Technological Design

Aside from species differences, the ability to compare results across studies is further complicated by methodologies used to assess airway remodeling. Airway remodeling is often quantified across large- and medium-sized airways by measuring airway wall thickness; however, bronchioles and other smaller bronchi, because of their diverse components and structures, may have different impacts on the evolution of airway remodeling. Even at the cellular level, distinct morphological, synthetic, and epigenetic differences between lung compartments exist, as has been described for fibroblasts isolated from airways compared with distal lung regions.^{173,174} Existing whole-organ/whole-body imaging modalities do not have enough resolution to distinguish particular cell types and can only assess various degrees of wall thickness.¹⁷⁰

Quantifying airway remodeling in human airways largely depends upon measuring indices within airway biopsy samples, or imaging modalities such as high-resolution computed tomography (HR-CT), both of which can predict fixed airflow obstruction in asthmatic patients.^{7,175} These techniques present challenges when attempting to study the longitudinal development and slow progression of airway remodeling in asthma patients due to either their invasive nature (biopsy) or high radiation exposure and cost (HR-CT). Several studies have suggested potential biomarkers of airway remodeling including TGF β and periostin,¹⁷⁶ galectin-3,¹⁷⁷ hyaluronan,¹⁷⁸ however, they have yet to be widely validated, which restricts their utility in clinical research. It is clear that both mechanistic studies of airway remodeling and clinical trials testing potential interventions that target airway remodeling remain incredibly difficult due to a lack of consensus on which AR index to use, cost effectiveness, safety, ability to make repeated measurements, plus sensitivity and specificity of measurement.

Concluding Remarks

As our understanding of the underlying mechanisms driving airway remodeling in asthma improves, so does our knowledge of how cell surface integrins play a critical role in the development and progression of airway remodeling. There is still much that we do not fully understand including the relative importance of mechanical and inflammatory cues to the development of airway remodeling. However, what is clear from research in recent years is that integrins may be involved in multiple aspects of airway remodeling across all lung cells types (see [Figure 1](#)). In the years to come, therapeutic targeting of airway remodeling may improve morbidity and lung function in patients with severe, uncontrolled asthma. With the advent of biological therapies in recent years we have begun to observe some positive effects on features of airway remodeling in the most severe asthmatics. Questions remain, however, about whether these effects are sufficient to produce long-term and long lasting impacts on airway remodeling that would improve fixed airflow obstruction and slow the decline in lung function that is observed in asthma. While the effects of some biologics on airway remodeling are encouraging we believe targeting airway remodeling specifically, rather than as a bi-product of targeting inflammatory pathways, will lead to the biggest clinical improvement in airway remodeling in the years to come. Such targeting could include approaches to target integrin mediated pathways since we have hopefully demonstrated in this review that integrins are integral to many pathways involved in airway remodeling pathogenesis. Targeting integrins directly to impact airway remodeling could be a useful adjunct to existing therapies that target airway inflammation to enable both fundamental features of asthma to be treated simultaneously.

Disclosure

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