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The Aftermath of Bronchoconstriction

Asthma is characterized by chronic airway inflammation, airway remodeling, and excessive constriction of the airway. Detailed investigation exploring inflammation and the role of immune cells has revealed a variety of possible mechanisms by which chronic inflammation drives asthma development. However, the underlying mechanisms of asthma pathogenesis still remain poorly understood. New evidence now suggests that mechanical stimuli that arise during bronchoconstriction may play a critical role in asthma development. In this article, we review the mechanical effect of bronchoconstriction and how these mechanical stresses contribute to airway remodeling independent of inflammation. [DOI: 10.1115/1.4042318]

Introduction

In 1917, D'Arcy Thompson first described in his book *On Growth and Form* how the size and shape of living organisms can be determined by physical force [1]. In the following century, scientists extensively studied the influence of different physical forces on cellular and organ function. It is now recognized that mechanical signals are a fundamental regulator of biological processes [2,3].

The lung is among the most dynamic organs in the human body. Through breathing, the lung is constantly exposed to the external environment which often includes environmental pollutants, bacteria, viruses, or allergens [4], which can provoke inflammation and activate signaling cascades that protect lung function ordinarily, but can disrupt lung function when they become dysregulated [5,6]. Moreover, with every respiratory cycle, lung volume changes considerably [7–9]. As a result, all cell types of diverse functions that reside in the lung are subjected to stretch and distortion [10–12]. These mechanical stresses have been shown to play critical roles in some of the most important biological processes in the lung [11,13,14]. For example, mechanical stress can guide branching morphogenesis and alveolar growth and thus results in the attainment of normal lung architecture later in life [15,16]. In addition, during lung development, both cell proliferation and differentiation can be promoted by mechanical stresses through the activation of signaling pathways that affect the production of extracellular matrix molecules and the expression of specific genes [17]. Unlike these ordinary mechanical stimuli, excessive mechanical stresses generated under certain pathological conditions not only impair protective functions but also lead to lung injury [9]. For example, application of mechanical ventilation is commonly used to support patients in respiratory distress [9]. In these patients, excessive mechanical stresses are transmitted across the pleural surface and alveolar wall to constituent cells, and the associated excessive mechanical stresses can cause ventilation-induced lung injury [18,19].

Here we focus on a rather different example: the mechanical effect of bronchoconstriction during asthmatic exacerbation. Asthma is a common, chronic respiratory disease with both environmental and genetic contributions to its pathogenesis [20]. It is estimated that 5–10% of the population in developed countries suffer from asthma and the prevalence increases by 50% every decade [21,22]. Asthma is characterized by chronic airway inflammation, airway remodeling, and excessive constriction of the airway [23]. As a common feature of asthma that causes symptoms,

constriction of the airway occurs due to the tightening of surrounding smooth muscle [24]. This may arise in response to a variety of causes including exercise, environmental exposure, and can be worsened by both recurrent infection and, in sensitized patients, allergen exposure [24–27]. Asthmatic bronchoconstriction may lead to consequent coughing, wheezing, and shortness of breath [20].

Currently, there is no cure for asthma [21]. Detailed investigation exploring the role of immune cell influx and pro-inflammatory mediators has revealed a variety of possible mechanisms by which the immune system drives airway remodeling processes [28,29]. The available treatments focusing on inflammation only controls the symptoms, which are frequently not improved by inhaled glucocorticoid treatment in severe asthma, and fatal asthma attacks usually result from a failed response of airway smooth muscle to relaxant drugs [21,23,26]. Moreover, recent evidence, including failure of clinical trials targeting inflammation, suggests that asthma can develop through inflammation-independent mechanisms [30,31]. These evidences suggest that the current treatments are not targeting the root cause of airway hyperresponsiveness and remodeling. On the other hand, lung structural cells themselves can also initiate airway remodeling. One of the important ways that lung structural cells contribute to asthma progression is through the biological and physical impact of these mechanical stresses induced by bronchoconstriction [19,32]. In the following content, we review the effect of compression on the airway epithelium and discuss the subsequent impact on progressive airway remodeling in asthma.

Asthmatic Bronchoconstriction and Epithelial Compression

During asthmatic bronchoconstriction, airway smooth muscle generates excessive mechanical force that can collapse the lumen [25,33], and subsequently, the lung structural cells within the airway experience considerable compressive stress. These cells form the air–tissue interface in the airways of all vertebrate species [34]. During a normal respiratory cycle, the transmural and trans-epithelial stresses are low and similar to transpulmonary pressure [35]. However, the associated mechanical stress, during bronchoconstriction, is considerably higher and can lead to airway wall buckling and the formation of rosette patterns [36]. Although the exact patterns of collapse during bronchoconstriction vary depending on the elements of airway wall, the pattern occurs due to the bicycle mechanical property of the basement membrane: stiff in extension but floppy in compression [36]. In asthmatics, the airway wall is thickened due to tissue remodeling [29,37]. Near the apex of the folding, the epithelial cells are opposed to each other and squeezed, exposing them to considerable

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compressive stress, especially during bronchoconstriction [36,37]. Wiggs and co-workers analyzed and estimated the magnitude of the mechanical stress on airway epithelial cells during asthmatic bronchoconstriction [37]. They estimated the mechanical properties of the two layers that were used to model the airway wall and theorized the hoop stress that airway smooth muscle would exert during maximal bronchoconstriction. Rosette patterns of deformation in the airway induced by bronchoconstriction were analyzed using finite element methods. They found that airway epithelial cells are subjected to ~ 30 cm H₂O compressive stress during maximal bronchoconstriction, which is thought to be at least an order of magnitude higher than the transepithelial stress on airway epithelial cells during normal respiratory cycle [37]. This change in the physical environment leads to altered biochemical properties, which represents an active area of investigation both in vitro and in vivo [19,32,38].

Mechanical Compression Induces Airway Remodeling Through Autocrine and Paracrine Epithelial Mechanisms

As airways narrow, the invagination of the epithelium leads to compression around the apex of the epithelial folds [37,39,40]. Ressler et al. first demonstrated that airway epithelial cells generate rapid and robust cellular responses after mechanical compression [40]. Using air-liquid interface-cultured rat tracheal epithelial cells, they found that after compression, epithelial cells express early growth response protein 1 (EGR), endothelin 1 (ET-1), and transforming growth factor beta 1. Tschumperlin and co-workers observed similar responses using primary human airway epithelial cells [41]. More importantly, they identified a novel mechanism of mechano-transduction, which combines the shedding of epidermal growth factor with a reduction in lateral space between epithelial cells during compression [41]. A subsequent study using computational modeling and analysis showed that constant rate shedding of autocrine ligands into a collapsing lateral intercellular space leads to increased local ligand concentrations that are sufficient to account for observed receptor signaling [42]. They found that the decrease in lateral intercellular space peaked at 10 min after compression, and the concentration of heparin-binding epidermal growth factor (HB-EGF) in the lateral intercellular space is increased [42]. The release of epidermal growth factor receptor ligand HB-EGF activates this G-protein-coupled receptor and downstream signaling ensues [41]. HB-EGF has been shown to lead to epithelial remodeling [43,44]. Another study examined the impact of epithelial compression on the epithelium itself. This diverse tissue contains several different cell types, including mucus-secreting goblet cells. Goblet cells are more abundant in the epithelium of asthmatic patients and play an important part in mucus hypersecretion [45]. Upon repetitive mechanical stress, cultured epithelial cells underwent goblet cell hyperplasia [46]. This mucus secretion increases the resistance of airways and, in some cases, can completely occlude the tubular structure.

Epithelial cells may also lead to airway remodeling through the release of paracrine mediators which can interact with nearby airway smooth muscle (ASM) cells, fibroblasts, and endothelial cells. It has been shown that epithelial cells drive the proliferation of nearby ASM cells, which could contribute to the increased mass of ASM in asthmatic patients [47–50]. Although the exact mechanism by which this occurs remains unknown, studies have shown that agonist and pro-inflammatory cytokines secreted from the epithelium could be the source. For example, using both in vitro and in vivo assays, Malavia et al. found that airway epithelial injury can modulate smooth muscle cell proliferation via a mechanism that involves secretion of soluble mediators including potential smooth muscle mitogens such as IL-6, IL-8, and MCP-1 [47]. The exposure of the epithelium to the common asthma-associated allergen house dust mite also led to increased ASM proliferation that was dependent on the release of cysteinyl leukotrienes [50]. Recent

in vitro evidence also suggests that epithelial compression induced by bronchoconstriction can also lead to ASM proliferation [48], just like repeat injury and allergen exposure [47,50].

The idea of an epithelial derived relaxing factor is a notion borrowed from vascular biology where the endothelium leads to relaxation of the vascular smooth muscle [51]. Indeed, a recent study demonstrated that epithelial–ASM cell co-culture led to a less contractile ASM cell [49]; however, this study utilized submerged (non-air–liquid interface) epithelial cultures. Another study showed that compressed epithelial cells induce ASM cell contractility through the release of the contractile agonist endothelin-1 (ET-1) [48]. Intriguingly, asthmatic human bronchial epithelial (HBE) cells led to a leftward shift in the dose-response curve of ET-1 release due to compressive stress [48]. This sensitivity of asthmatic epithelium to mechanical forces may represent a previously unidentified mechanism by which asthmatic HBE cells lead to ASM remodeling. The mechanism proposed also involves a feed-forward loop through which smooth muscle mass and contractility are correlated with compressed epithelial cells, which in turn could perpetuate this loop [48]. Further, when HBE cells were cultured from asthmatic subjects, the HBE cells induced differences in the contractile responses of ASM cells at lower magnitudes of compressive stress [48]. This implicates the asthmatic epithelium as a hyper-responsive tissue exposed to the compressive environment of the diseased airway and further strengthens the link between bronchoconstriction and airway remodeling. Lan et al. also observed an increased proliferation in ASM cells that were cultured in compressed epithelial conditioned medium [48], indicating that these two phenotypes can co-exist.

Basement membrane thickening, through release of extracellular matrix proteins, is another feature of airway remodeling in asthmatic patients [52,53]. Extracellular matrix provides rigidity to the airway structure and so the implications of increased matrix thickening remain somewhat of a mystery. Increased bulk tissue within the contractile element of the airway could contribute to smaller airways and therefore increased resistance; however, increased rigidity would oppose the contractile effect of smooth muscle [54]. Increased collagen surrounding the airway tree was speculated to prevent the efficacy of glucocorticoid administered to act upon proliferating ASM cells [55] and may prevent the access of pharmacological therapeutics to ASM. Nearly 20 years ago, Swartz et al. demonstrated that epithelial–fibroblast co-cultures produced more type III collagen when the epithelial cells had been exposed to mechanical compression prior to the co-culture [56]. Although the mechanism was unclear, this seminal study laid the ground work for several important subsequent publications. Choe et al. showed that lateral compressive strain applied to tissue-engineered airways leads to the production of collagen types III and IV [57]. The extracellular matrix may also contribute to the remodeling of ASM, as asthmatic ASM cells were shown to produce more collagen I and perlecan than cells cultured from healthy subjects, and these matrix proteins lead to a more proliferative ASM cell [58]. The native, nonconstricted epithelium has been well described to induce proliferative responses in airway smooth muscle cells. Some work suggests that proliferating smooth muscle is in a reduced-contractile state due to the pleiotropic transcription factors that control these fates [59]; however, more work in this area needs to be conducted.

The compressive stress induced by bronchoconstriction can also lead to the release of extracellular vesicles from HBE cells [60]. Furthermore, these vesicles contained pro-remodeling factors such as tissue factor [60], implicating them as a potential method by which the compressed epithelium could influence other cell types. The pro-inflammatory and asthma-associated type 2 cytokine IL-13 magnified the release of compressive stress-induced tissue factor [61], indicating the potential interaction of immune cell mediators and compressed epithelial remodeling potential. Although unexplored to date, the interaction of recruited leukocytes and the epithelium in this altered physical environment will require future investigation to better understand the pathophysiology of asthma and other lung diseases.

Much of the pioneering work in the field of epithelial compression-regulated airway remodeling was performed on air–liquid interface cultures. However, excitingly, Grainge et al. conducted a study on human subjects to uncover the role of airway narrowing on airway remodeling [62]. Asthmatic subjects who were challenged with methacholine, a bronchoconstrictor, demonstrated increased goblet cell hyperplasia and increased thickening of the basement membrane [62]. As controls, some patients were given a beta-agonist prior to the administration of methacholine to keep the airways relaxed [62]. This confirmed prior *in vitro* work and critically informed the field of the importance of preventing asthma exacerbation to hinder further airway remodeling processes. Yet, these evidences were primarily based on biopsies. On the other hand, Janssen et al. found that repeated methacholine challenge over the course of 3 years did not result in significant changes in lung function [63]. It is possible that the impact of airway remodeling presented by Grainge et al. may not be large enough to change lung function. A similar study was performed in BALB/c mice to assess the influence of multiple constriction events on airway mechanics and remodeling [64]. Surprisingly, 48 h after the final administration of methacholine, the airway mechanical responses to methacholine were unchanged, as was a majority of readouts for airway remodeling [64]. However, goblet cell hyperplasia was indeed observed [64]. This also highlights the interspecies variability of these systems and suggests one should be cautious when drawing comparisons from mouse models of airway disease to asthma in human subjects. There are clearly diverse mechanisms by which compression of the airway wall can lead to remodeling of the airways and contribute to disease pathogenesis. The remodeling events induced by bronchoconstriction are likely to be complex in nature. Although *in vitro* studies demonstrate promising results of compression induced airway remodeling, it is worth noting that more *in vivo* studies are necessary to better illustrate this process. In addition, the number of studies using animal models to investigate airway remodeling events is also rather limited. Further work examining the intricacies of these signaling pathways in three-dimensional tissue cultures, animals, and humans is necessary to better understand the process by which the asthmatic airway becomes remodeled.

Mechanical Compression and Unjamming of Airway Epithelial Cells

Airway epithelium is dysregulated in asthma, typified by an aberrant injury-repair response [65]. However, the cause of dysregulated epithelium remains unclear. Dysregulation of the airway epithelium has been attributed to downstream effects of an upstream cascade of immune and inflammatory events, such as type 2 inflammation. However, since coordinated communication between biochemical and mechanical signals guides the function of the epithelium, it is possible that mechanical stimuli, like epithelial compression, may also connect to the deregulated epithelial cells in asthma. Recent evidence from Park and co-workers discovered that the maturing epithelial cells in air–liquid interface culture undergoes a transition from a fluid-like, migratory unjammed state to a solid-like, quiescent, jammed state through a process referred to as a jamming transition, which is delayed in cells cultured from asthmatic subjects [66]. Whether this delay arises from layer injury, immaturity, or dysmaturity remains unclear. However, it has been shown that the unique dynamic features of the jamming transition are deeply connected to cell shape [66,67]. More importantly, the jamming and unjamming transitions, with universal signature in cell shape and variation, can be found in many other important processes of epithelial biology, including embryo development and cancer invasion [67–70]. Park and colleagues also found that application of an apical-to-basal mechanical stress mimicking the compressive effect of bronchoconstriction can trigger the unjamming transition in a pseudostratified primary human bronchial epithelial layer [66]. This suggests

that mechanical compression itself could be an important contributor to the unjammed epithelial cells in asthmatics. Further studies exploring the connection between cell jamming in airway epithelial cells and airway remodeling are necessary to determine its role in asthma.

Where Do We Go From Here?

Even in the absence of inflammatory cells or mediators, the mechanical aftermath of bronchoconstriction, *in vitro* and *in vivo* compression on airway epithelium is sufficient to initiate airway remodeling [46,48,62,71]. Moreover, the compressive effect on the epithelium, induced by bronchoconstriction, can lead to increased smooth muscle mass and contraction [49], which can further increase the degree of constriction, suggesting that there may be a potential positive feedback loop of bronchoconstriction in asthmatics (Fig. 1). Thus, breaking this viscous loop could be an effective way to control airway remodeling progression. Surprisingly, the best defense system against bronchoconstriction is already in our body. In 1864, Henry Salter first described that constriction of the airway can be broken by simply taking a long, deep, full inspiration [72]. Until this day, a simple deep inspiration (DI), which occurs roughly six times per hour [72,73], is still the most effective bronchodilator known [74–78]. Further studies suggest that a DI can also protect the airway and prevent subsequent constriction [76,79–82]. However, the beneficial effect of DI is impaired in the asthmatics. Numerous studies demonstrated that DI-induced bronchodilation and stretch are dependent on the activation state of ASM [83–85]. More activation in ASM leads to less strain and less relaxation for any given tidal volume. Thus, it is likely that the airways in asthmatic patients cannot bronchodilate due to the undergoing asthmatic exacerbation. This could lead to prolonged compression of the airway epithelial tissue in asthmatics, which in turn will likely lead to further airway remodeling.

Despite the contrary evidence [83,86,87], the preponderance of experimental evidence obtained *in vitro*, *ex vivo*, and *in vivo* confirm a potent dilation effect on airway smooth muscle by mechanical stretch mimicking DI [72,77,84,88–94]. In response to a transient stretch, the cytoskeleton of airway smooth muscle undergoes a rapid transition from a solid contractile state to a fluid-like relax state, termed fluidization [92,95,96]. Targeting fluidization may perhaps restore the impaired bronchodilator effect in asthmatics. Although the mechanism of fluidization transition is still

Fig. 1 Bronchoconstriction can recapitulate key phenotypic changes of asthmatic airway remodeling through mechanical compression on epithelium. These changes include goblet cell hyperplasia, thickening of the basement membrane, airway smooth muscle proliferation, and contraction. These findings suggest that there is a potential vicious positive cycle of bronchoconstriction which contributes to the progression of asthma, independent of inflammation.

unclear, it has been shown that the disruption of actomyosin during transient stretch is an important contributor to fluidization [89,91,92,97]. Recent evidence from Lan and co-workers suggest that cofilin, an actin severing protein, plays a critical role in the fluidization response [98]. Thus, it is possible that cofilin and its associated signaling pathway may hold the key to break the vicious cycle of bronchoconstriction.

As a feature of asthma, bronchoconstriction has frequently been considered as a symptom, whereas its role in asthma development has been overlooked. This view needs to be reconsidered as a better strategy of bronchoconstriction management could lead to a better control of the asthma development, especially airway remodeling. In fact, new therapeutic approaches combining sustained bronchoprotection and anti-inflammatory treatments suggest that long-acting β_2 -agonist combined with corticosteroid administration is a far more effective treatment of asthma than high doses of corticosteroid alone [99–101]. In addition to symptom control, combination treatment can also improve the signs of airway remodeling, such as decreasing in the number of myofibroblasts and airway smooth muscle mass [102]. Although the combination of long-acting β_2 -agonist and inhaled corticosteroid demonstrate promising results, bronchoconstriction is certainly not the sole mechanism behind remodeling and asthma exacerbation. Thus, one important open question remains concerning the unknown roles of bronchoconstriction in inflammation and innate immune responses. A few studies suggest that compression can indeed lead to elevated IL-8 and NF-KB [103,104]; however, the mechanisms of such increases are still unknown.

The mechanical consequence of bronchoconstriction is complex in nature and it is likely that compression is not the only mechanical event during this process. However, apical-basal compression was used in all in vitro studies to explore the compression effect on airway epithelium [41,46,48,60,61,66,71]. As the airway narrows, the epithelial cells are compressed at the apex of the folding position, but it is also worth pointing out that some of the epithelial cells are stretched at the tip of the folding. Thus, one question of particular interest is what is the effect of stretch on airway epithelium and airway remodeling? Interestingly, mechanical stretch has been shown to induce unjamming in other types of epithelial cells, just like mechanical compression [67]. Thus, it is possible that mechanical stretch on airway epithelium may also contribute to airway remodeling, just like mechanical compression.

In summary, extensive evidence from both in vitro and in vivo studies demonstrated that mechanical aftermath of bronchoconstriction can recapitulate key phenotypic changes of asthmatic airway remodeling, including thickening of subepithelial collagen layer and goblet cell hyperplasia [33,47,57,61–63]. Although there is no direct evidence from in vivo studies, new in vitro evidence suggests that mechanical force induced by bronchoconstriction can also lead to ASM proliferation and contraction in culture [49]. Taken together, these data suggest that there is a potential vicious positive cycle of bronchoconstriction that drives the worsening of asthma independent of inflammation. Thus, bronchoconstriction is not simply a consequence or symptom of asthma and should be considered an important contributor to airway remodeling and asthma development.

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