Collagen in Airway Mechanics

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Collagen is the most abundant airway extracellular matrix component and is the primary determinant of mechanical airway properties. Abnormal airway collagen deposition is associated with the pathogenesis and progression of airway disease.

collagen airway mechanics

1. Introduction

The airway consists of both a conducting region (larynx, trachea, bronchi, bronchioles) where air is humidified, warmed, and cleaned and a respiratory zone where gas exchange occurs. The airway is directly and continuously exposed to both macromechanical and micromechanical forces. Macromechanics is the study of organ-level mechanical and material properties. Intrathoracic respiratory forces, perfusion, and cough represent some of the dynamic macromechanical forces exerted on the respiratory system. As the airway is composed of heterogeneous components (chondrocytes, epithelium, endothelium, muscle, extracellular matrix (ECM)), these constituents can be individually quantified using micromechanics. Micromechanical properties drive the mechanotransduction in the airway, driving cell-cell and cell-matrix interactions [1].

The collagen family is the most abundant component of the airway ECM [2][3][4][5], providing structural support and facilitating cell adhesion and tissue development [6]. Diverse collagen subtypes are represented throughout the airway: Type IV collagen is the chief component of the basement membrane [7], type II collagen predominates in airway cartilage, and type I and III collagen are found in the alveolar wall and alveolar septa [8]. Due to their abundance in the alveoli, type I and III collagen are the primary contributors to lung mechanics [2][7][9]. Collagen homeostasis is dynamic and can be influenced by injury, repair, and pathologic change [10][11][12]. As a result, byproducts from collagen synthesis and degradation can serve as biomarkers for disease progression.

2. Collagen Determines Airway Mechanics

The primary role of collagen is to provide tensile strength to the ECM [13][14], with collagen subtypes assuming different roles in airway tissue (Table 1). With 28 different subtypes of collagen, subtypes I, II, and III predominate, representing 80%~90% of total collagen [15][16]. In the airway ECM, type I collagen provides mechanical stability and structure. Type II collagen is the major component of airway cartilage (95% of total collagen), facilitating chondrocyte synthesis of ECM [17][18][19]. Type I and III collagens provide structural framework in the bronchi, interstitium, and alveolar wall [20][21][22]. Type III collagen in the airway is flexible, existing as narrow fibrils, and is

more susceptible to breakdown than other fibrillar collagens [10][12][23]. Together, the collagen type I / type III ratio determines the resistance of collagen fibers to breakdown under mechanical forces during stretching [2]. Type IV collagen fiber is fundamental for maintaining the strength and function of the basement membranes [24][25].

Table 1. Role of the different types of collagen in airway.

Collagen Subtype	Collagen's Role
Type I collagen	· a primary contributor to lung mechanics · provides mechanical stability and structure · provides a structural framework in the bronchi, interstitium, and alveolar wall
Type II collagen	· the major component of airway cartilage (95% of total collagen) · facilitates chondrocyte synthesis of extracellular matrix (ECM)
Type III collagen	· a primary contributor to lung mechanics · provides a structural framework in the bronchi, interstitium, and alveolar wall
Type IV collagen	· fundamental for maintaining the strength and function of the basement membranes
Collagen type I / type III ratio	· determines the resistance of collagen fibers to breakdown under mechanical forces during stretching

As the primary structural component of airway ECM, collagen provides biomechanical cues for cell adhesion and tissue growth [6]. Studies of ECM mechanics in pulmonary diseases suggest that collagen is the most important load-bearing component of the lung parenchyma and has an essential role in maintaining tissue homeostasis and mediating cellular responses to injury [2]. Mechanical cues within collagen matrices serve to organize cell

arrangement in the ECM: these cues facilitate cell alignment and cell-matrix bundling of collagen; conversely, pathologic changes in collagen fibril formation can prevent cell alignment and cell polarity [26].

Collagens also play a vital role during airway regeneration and repair. Regenerative medicine has adopted the use of acellular airway constructs through decellularization in an effort to provide a biomimetic scaffold for tissue engineering. However, decellularization of a multi-lineage tissue (bearing epithelial, vascular, muscle, and cartilaginous structures) such as the trachea has resulted in ECM injury, loss of graft mechanical properties, and collapse in both pre-clinical and clinical applications [27][28]. New approaches to tracheal tissue engineering have focused on the preservation of the native ECM, most importantly its collagen content [29][30].

3. The Role of Collagen in Airway Disease and Disease-Associated ECM Stiffness Change

In airway diseases, abnormal tissue remodeling is associated with the deposition of ECM components such as collagens, fibronectins, and proteoglycans, in and around the epithelium and surrounding vessels [31][32][33][34]. Pathologic collagen remodeling involves the reorientation and rearrangement of fibers in an effort to confer greater strength to the region of injury. With the high prevalence of collagen in the airway, its deposition or degradation is a surrogate for the stiffness change observed in airway disease. Burgeoning research in collagen homeostasis has the potential to identify biomarkers in the early diagnosis and treatment of lung diseases.

3.1. Increased Collagen Concentration in Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease that causes alterations in the cystic fibrosis transmembrane conductance regulator (CFTR) chloride ion channel, leading to thick mucus blocking the airway, causing infections and scarring of the lung [35]. This results in an alteration of cellular and matrix stiffness. Human epithelial cells derived from patients' airways with CF and CFTR mutant cells have been found to have a lower Young's modulus than normal human epithelial cells [36][37]. Alveolar matrix remodeling and fibrosis is present in the CF lung and leads to stiffening of alveolar tissues. In patients with CF, collagen I and elastin concentration in alveolar septa were increased ~9-fold and~5-fold, respectively, as compared to healthy controls [38].

3.2. Collagen Deposition in Asthma

Asthma is a chronic inflammation of the airway that leads to episodic narrowing of the airway, which is commonly exercise- or allergen-induced [38]. Over time, hyper-responsiveness of the airway leads to inflammation and airway remodeling. With airway remodeling in asthma, collagen deposition results in an increase in matrix stiffness [[39][40]. Early in vivo studies on patients with asthma have found increased collagen at the bronchial submucosal level; increased deposition of type I, III, and V collagens in asthmatic airways is well established [41][42][43]. This pathologic collagen deposition contributes to fibrosis, which can contribute to disease progression and severity in

asthma [44][45]. Beyond disease severity, genetic factors also play a role in matrix collagen content and subsequent lung mechanics [46].

The correlation between collagen deposition and ECM stiffness has also been studied in vitro. Human bronchial fibroblasts (HBF) derived from asthmatic patients had a higher elastic modulus compared to non-asthmatic HBF [47]. Asthmatic airway smooth muscle cells (ASMCs) secrete more collagen I and less collagen IV than non-asthmatic ASMCs [48]. ASMC-mediated collagen remodeling can be used to screen treatment to asthma by monitoring contraction and degradation of collagen [49]. In turn, when cultured in collagen substrates with higher stiffness (93 kPa) than control (23.1 kPa), ASMCs exhibited behaviors (e.g., stimulated proliferation) similar to asthma [50]. This suggests that the maintenance of normal lung stiffness is essential to maintain native ASMC expression. Notably, myofibroblasts, an intermediate between fibroblasts and smooth muscle cells, and fibroblast-to-myofibroblast transition (FMT) contribute to progression of fibrosis in asthma. Transforming Growth Factor-Beta (TGF-β) induced FMT and ECM stiffness in asthma exits as a vicious cycle: increased ECM stiffness causes enhanced FMT, which in turn leads to increased secretion of collagen, resulting in a reciprocal increase in matrix stiffness [51][52][53][54]. Thus, the interruption of this cycle by decreasing collagen secretion or blocking FMT may be a target in future asthma therapeutics.

3.3. Enhanced Collagen Deposition in Idiopathic Pulmonary Fibrosis is Associated with the Increased ECM Stiffness

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial pneumonia of unknown cause [55]. The incidence of IPF rises with age and carries a poor prognosis with a mean survival after diagnosis of 3 years [56]. Advances in defining the mechanisms of IPF describe a sequence of events that result in disease development: genetic predispositions, chronic epithelial cell turnover, and environmental exposures that ultimately lead to epithelial dysfunction [56]. Collagen has a prominent role in the pathogenesis of disease; deposits in the alveolar walls progressively destroy normal alveolar architecture [57][58]. From a mechanical perspective, decellularized and native IPF samples displayed higher stiffness than healthy lung samples [59]. The Young's moduli derived from AFM and a low-load compression testing are listed in Table 3. Mass spectrometry revealed that the IPF acellular lung also exhibited a different matrisome profile (collection of ECM components/proteins) exclusively expressed type I, V, and XV collagens, and was composed of higher amounts of type III, IV, VIII, and XIV collagens than normal tissue [60]. This suggests the role of increased collagen deposition in IPF is associated with the enhanced stiffness in the ECM. Homeostasis type I collagen is believed to have an essential role in IPF pathogenesis. TGF-β1 upregulates collagen I expression in fibroblasts cultured in 3D-collagen I gels [61]. Further, type I collagen upregulation was higher in fibroblasts derived from patients with IPF than from healthy controls [61] The amount and stiffness of collagen fibers from IPF lung tissue were found to be similar to healthy tissue. However, lysyl oxidase (LOX) enzymes (responsible for collagen's post-translational modification) were upregulated in primary human lung fibroblasts from patients with IPF. LOX inhibition normalized the dysregulated post-translational collagen cross-linking and reduced tissue stiffness [62]. Rather than increased deposition, Jones et al. believed that altered collagen architecture determined tissue stiffness in IPF [62].

3.4. Collagen I and III Are Remodeling Markers in COPD

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the lungs, manifesting as incomplete airflow obstruction resulting in emphysema and chronic bronchitis [63]. Typically resulting from tobacco smoke or other inhalational injuries, COPD results from narrowing and inflammation of small airways as the emphysematous lung loses its elasticity, resulting in dyspnea, cough, and excessive sputum production. Innate and adaptive immune responses and disruptions in ECM remodeling result in airway and alveolar remodeling. In 2019, Ito et al. provided a comprehensive review of ECM change in COPD and the role of type I and III collagen as biomarkers for remodeling [64]. In patients with COPD, Kranenburg et al. demonstrated an increased expression of total collagens I, III, and IV in the basement membrane and an increased expression of collagens I and III in bronchial lamina propria and adventitia [65].

As mentioned previously, emphysema is part of the pathophysiology of COPD [66]. ASMC proliferation is affected by ECM stiffness, resulting in smooth muscle loss and matrix softening in small and terminal airways of patients with emphysema [67]. Diseased lung presented higher collagen content and altered airway mechanics than normal lung, with lower dynamic tissue elastance as well as hysterisivity in a mouse model of emphysema [68]. Collagen fibers were found to be 24% thicker in rat lung with elastase-induced emphysema. In addition, the threshold of collagen to maintain mechanical stability is reduced, demonstrated by broken collagen fibers under similar stretch [69]. These findings suggest abnormal collagen remodeling has a significant role in COPD lung mechanics.

3.5. Collagen I and III Are Associated with Lung Mechanics Change in Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a condition where the alveoli or alveolar vessels are injured, leading to inflammation and increased fluid in the alveoli. In patients with ARDS, mechanical ventilation can cause additional lung injury due to the barotrauma from high airway pressures [98,99]. In ARDS, collagens can serve as markers of remodeling in various regions of the airway [8]. Excessive type I and III collagens can be detected in interstitial edema. ARDS matrix remodeling in ARDS requires myofibroblast migration or contraction generating mechanical forces, which deposit type III collagen during the early stages of ARDS. In later stages of disease, there is an increase in type I collagen and collagenase-digested type III collagen, leading to a tendency towards fibrosis [8]. In animal models of early acute lung injury (a milder type of ARDS), tissue resistance and dynamic elastance increased in rat lung parenchymal strips. These mechanical properties were persistently high at the late stage; meanwhile, collagen fiber content increased exponentially with the injury's severity [10].

3.6. Aging is a Factor of Collagen Alteration in Lung

Lung function is known to deteriorate with age, resulting in poorer mucociliary clearance, loss of elastic recoil, and poorer lung function on PFT. One mechanism of lung aging is increased collagen and decreased elastin production by fibroblasts, thus increasing pulmonary stiffness and lowering compliance, increasing the elastic modulus [70][71]. In addition to changes in the quantity of certain matrix proteins, collagen undergoes post-translational

modifications, increasing collagen cross-linking and thereby increasing rigidity while decreasing fiber length and width. These changes in collagen mechanical properties can influence response to therapeutics [72][73].

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