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Recent Advances and New Opportunities in Lung Mechanobiology

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Abstract

Lung function is inextricably linked to mechanics. On short timescales every breath generates dynamic cycles of cell and matrix stretch, along with convection of fluids in the airways and vasculature. Perturbations such airway smooth muscle shortening or surfactant dysfunction rapidly alter respiratory mechanics, with profound influence on lung function. On longer timescales, lung development, maturation, and remodeling all strongly depend on cues from the mechanical environment. Thus mechanics has long played a central role in our developing understanding of lung biology and respiratory physiology. This concise review focuses on progress over the past five years in elucidating the molecular origins of lung mechanical behavior, and the cellular signaling events triggered by mechanical perturbations that contribute to lung development, homeostasis, and injury. Special emphasis is placed on the tools and approaches opening new avenues for investigation of lung behavior at integrative cellular and molecular scales. We conclude with a brief summary of selected opportunities and challenges that lie ahead for the lung mechanobiology research community.

Keywords

mechanotransduction; extracellular matrix; respiratory; stretch

The evolution of lung mechanobiology

The core function of the lung, to facilitate the exchange of gases between the circulation and the external environment, is inextricably linked with mechanics. Respiratory muscles generate a transpulmonary pressure gradient, prompting gas to flow through the branched structure of the airways to alveoli whose stability depends on a fine balance of tissue and surface forces (Fredberg and Kamm 2006), while blood from the heart circulates through a dense network of capillaries to exchange CO_2 and O_2 across the delicate alveolar-capillary walls (Maina and West 2005). Understanding the physical origins of these functions, and their failure in various disease states, has been central to the study of respiratory physiology and medicine since the inception of these fields. Seminal historical developments, such as the characterization of pulmonary surfactant function (Obladen 2005), helped to reveal the central role of mechanics

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in lung function. Current mechanobiological study of the lung thus builds on a long history and a rich foundation. This review focuses on recent progress over the preceding five years, emphasizing new tools and approaches driving progress in the field, and new insights into molecular, cellular and microstructural aspects of the biology-mechanics interface helping to inform our evolving understanding of lung function in health and disease.

Imaging tools open new doors

Mechanobiological study of the lung requires a detailed understanding of the mechanical state of the tissue under physiological conditions. The delicate and complex microstructure of the lung, encased within the thoracic cavity, has posed a long-standing challenge in terms of access for imaging and measurement. Traditionally, measurements of lung mechanics and attribution of mechanical contributions to various anatomical or tissue components have been inferred from pressure, volume, and flow relationships obtained at the entrance to the airways. While great strides have been made in extracting information from these measurements, new advances in methods to visualize the microstructure and dynamics of living lung tissue are opening exciting new opportunities.

At the macro-scale, application of non-invasive imaging modalities are providing new information about regional tissue deformations and may make possible local measurements of intact lung mechanical properties. For instance, microfocal x-ray imaging of airways is allowing unprecedented measurements of airway dimensions in intact lungs (Fig. 1A), providing new insight into regional, axial and circumferential variations in airway strains that occur with changing lung volume (Sera et al. 2004;Sinclair et al. 2007). Magnetic resonance elastography (MRE) is a technique that is well-established as a non-invasive means to sample tissue mechanics in soft organs such as the liver. While application of MRE to the lung is complicated by its air-filled structure, preliminary work using porcine lungs inflated with hyperpolarized ^{3}He validates the feasibility of applying this methodology to measure tissue mechanical properties within intact lungs (McGee et al. 2008).

At the micro-scale, recent advances have brought the power of microscopy to the visualization of internal lung microstructure. While limited to the peripheral subpleural region of lung tissue, intravital microscopy has opened new opportunities to visualize events within the alveoli and microvasculature of the intact lung (Kuebler et al. 2007). Exciting opportunities now exist to couple such imaging tools with fluorescence indicators of cellular signaling events allowing the study of mechanotransduction in situ (Kuebler et al. 2007; Sabouri-Ghomi et al. 2008). Moreover, intravital imaging approaches are leading the way towards an increasingly sophisticated understanding of local mechanical properties and deformations in the intact lung (Popp et al. 2006; Perlman and Bhattacharya 2007).

One example of the way intravital microscopy has already enriched our understanding of local intra-alveolar deformations comes from confocal imaging of subpleural alveoli in isolated rat lungs (Perlman and Bhattacharya 2007). This study demonstrated striking heterogeneity in the behavior of alveolar wall segments (Fig. 1B), with greater distention observed in wall segments associated with type I epithelial cells than in those segments associated with type II epithelial cells (Perlman and Bhattacharya 2007). Type II cells are more vulnerable to cell injury and or death when stretched than are type I cells (Tschumperlin and Margulies 1998). Together these findings suggest that the alveolus is designed to protect type II cells from large distention, either through geometric or compositional effects on the underlying matrix, or through changes in the stiffness of the individual cell types themselves. Support for the latter comes from application of atomic force microscopy (AFM) to isolated lung epithelial cells, where it was observed that the cytoplasm of type II cells is stiffer (~2-fold median difference) than that of type I cells (Azeloglu et al. 2008).

AFM, while more invasive than the methods described above, provides a unique perspective because it can characterize cell and tissue mechanical properties with micron-scale spatial resolution. Recently, AFM was used to map the local elasticity of migrating epithelial cells in a model of wound healing (Wagh et al. 2008), demonstrating the great potential for AFM to probe cellular and subcellular mechanics in isolated cells (Gavara et al. 2008; Kang et al. 2008). But AFM has also been used to characterize the local mechanical properties of intact soft tissues (Engler et al. 2004; Berry et al. 2006; Engler et al. 2007). We have employed AFM microindentation to spatially map the stiffness of lung tissue slices harvested from mice with bleomycin-induced fibrosis (Fig. 2A, unpublished data). Prior measurements of lung tissue at the macro-scale indicated an approximate doubling or tripling of tissue stiffness with fibrosis (Dolhnikoff et al. 1999; Ebihara et al. 2000). In contrast, AFM microindentation reveals that tissue stiffening is highly localized, with some regions up to ~30-fold stiffer than the median observed in normal lung tissue. Given the profound effects matrix stiffness can exert on fibroblasts (Wang et al. 2000; Goffin et al. 2006; Li et al. 2007; Wipff et al. 2007), it's likely that lung remodeling and changes in matrix rigidity play a prominent role in various pathologies of the lung, including asthmatic airway remodeling, fibrosis, emphysema, and pulmonary hypertension. So far the role of matrix stiffness in the initiation and amplification of these lung diseases remains largely unexplored.

Micro-scale and multi-scale mechanics

A major goal of lung mechanobiology is to understand how the mechanical behavior of the lung emerges from its molecular and cellular constituents (Suki and Bates 2008). Cell-matrix model systems have been used to identify the stimuli that promote cell-mediated matrix remodeling, and concomitant changes in matrix organization and mechanical behavior (Leung et al. 2007; Raub et al. 2007; Raub et al. 2008). Analysis of second harmonic generation from multi-photon imaging of cell-matrix constructs (Raub et al. 2007; Raub et al. 2008) is being used to explore linkages between structural and mechanical properties of collagen matrices. Mechanical testing of lung tissue strips, coupled to selective perturbation of matrix constituents, is advancing our understanding of how collagen, elastin and other matrix proteins contribute to tissue stability and deformability (Kononov et al. 2001; Cavalcante et al. 2005; Jesudason et al. 2007). Similarly, lungs from mice genetically deficient for the proteoglycan decorin support a prominent role of this matrix protein in lung mechanics (Fust et al. 2005). These studies are challenging the long held assumption that lung mechanics can be simply partitioned into contributions from elastin at low volume, and collagen at high volume. Based on compelling evidence that alveolar walls can fail under loading, particularly when the matrix is remodeled (Kononov et al. 2001; Ito et al. 2004; Ito et al. 2005; Ito et al. 2006; Ritter et al. 2009), Suki and colleagues have put forward a compelling hypothesis (Fig. 2B) to explain progressive emphysema based on percolation of sequential alveolar wall rupture (Suki et al. 2005; Bates et al. 2007; Suki and Bates 2008). Together these approaches are building a multi-level hierarchical understanding of lung tissue mechanics, moving toward the ultimate goal of predictive power to understand how molecular perturbations alter lung micromechanics.

In parallel with advances in solid mechanics, ongoing investigations of biofluid mechanics in the pulmonary system (Bertram and Gaver 2005) are providing an improved understanding of lung injury mechanisms associated with closure and opening of fragile tissue structures (Kay et al. 2004; Yalcin et al. 2007), and generating multi-scale models for investigation of fluid dynamics in airways and lung vasculature (Tawhai and Burrowes 2008). At the interface of solid and fluid surfaces, recent experimental work has demonstrated that the airway-lining layer of mucus, which is optimized for lung defense and clearance, is responsive to airway shear stresses (Tarran et al. 2005; Tarran et al. 2006), and that pathological changes in mucus viscoelasticity can be targeted as a new therapeutic modality for patients with cystic fibrosis (Donaldson et al. 2006; Tarran et al. 2007).

Flow resistance through the airways is highly responsive to the dimensions of airways, which can be dynamically regulated by airway smooth muscle contraction. Because airway narrowing compromises efficient gas transport, the dysregulation of airway dimensions represents a critical pathogenetic mechanism in both asthma and chronic obstructive pulmonary disease (COPD). Over the past decade the demonstration that airway smooth muscle tone is dynamically equilibrated, and thus sensitive to lung volume history, represents a major advance in lung mechanobiology (An et al. 2007). However, fundamental questions remain regarding mechanisms of airways hyperresponsiveness, and whether the locus of hyperresponsiveness is the smooth muscle itself, the remodeled airway, matrix or cellular constituents, or some combination (McParland et al. 2003; Wagers et al. 2004; Bates and Lauzon 2007; James and Wenzel 2007; Wagers et al. 2007).

Stretching the lung

The effects of stretch, as the central physical change required for lung inflation, continues to dominate lung mechanobiological investigation at organ and cellular scales. At the whole organ scale the effects of stretch are manifested in three major settings: lung development, compensatory growth, and injury.

During lung development in utero the epithelium is secretory, in contrast to its absorptive role in mature lungs. Lumenal secretions across the epithelium flow through the developing airways and exit through the larynx and nasopharynx where the partial occlusion of the vocal cords acts as a one way valve that generates back pressure to partially inflate the growing lungs. This tonic inflation is critical to lung development, as failure to inflate retards lung growth and maturation (Tschumperlin and Drazen 2006). Tracheal occlusion increases lumenal expansion, and accelerates branching and cellular maturation (Unbekandt et al. 2008). Recent experiments using organ cultures of primitive lung buds and perturbations targeting actin-myosin contractility demonstrate a critical role for local force generation in branching morphogenesis (Moore et al. 2002; Moore et al. 2005). While the organ-level response to tracheal occlusion is well documented, the dissection of the cellular events that follow tracheal occlusion is only recently begun with the demonstration of rapid increases in proliferation of both epithelial and mesenchymal cells (Seaborn et al. 2008). Further efforts directed at elucidating the molecular mechanisms coupling tracheal occlusion to accelerated airway branching point to the FGF10-FGFR2b signaling axis (Unbekandt et al. 2008). Similar to effects on airway branching, lung distention has also recently been shown to play a pivotal role in coordinating angiogenesis in the developing lung (Cloutier et al. 2008).

Based on the essential role for mechanical forces in lung development, it is not surprising that mechanical forces also play a leading role in the compensatory growth of the lung following surgical resection (2004; Hsia 2004). Thus harnessing the mechanical environment therapeutically could represent a powerful stimulus to treat hypoplastic lungs (Butter et al. 2005) or regenerate functional lung units lost to aging and disease (Fehrenbach et al. 2008). Unfortunately, the robust compensatory growth seen in rodents and young animals is much weaker in adults (2004), and attempts to augment compensatory growth have met with mostly frustrating results (Dane et al. 2004; Ravikumar et al. 2007). The recent description of resident stem cells in a number of lung niches (Rawlins and Hogan 2006; Stripp and Shapiro 2006; Kim 2007), and the possible connection between mechanical stimulation and stem cell activation (Nolen-Walston et al. 2008) offers some hope that mechanobiological approaches may someday help to unlock the lung's inherent regenerative capacity.

On the flip-side of regeneration, a vast body of literature demonstrates potentially pathological responses to lung stretch (Oeckler and Hubmayr 2007), culminating in clinical trials demonstrating protective effects of reducing tidal volume during mechanical ventilation (2000;

Meade et al. 2008). Recently, experimental studies have explored how even moderate volume ventilation, when superimposed on existing pulmonary conditions, can result in deleterious effects on lung function (Altemeier et al. 2004; Altemeier et al. 2005; Bregeon et al. 2005; Tsuchida et al. 2005; Dhanireddy et al. 2006; Levine et al. 2006; O'Mahony et al. 2006; Tsuchida et al. 2006).

Intense research efforts continue into the molecular mechanisms that couple ventilatory stresses and strains into adverse physiological outcomes. Recently, TRPV4 (Hamanaka et al. 2007) PI3K, Akt and Src (Miyahara et al. 2007) have been implicated in capillary leakage, while hyaluronan fragmentation was implicated in IL-8 upregulation (Mascarenhas et al. 2004), and cellular stress failure demonstrated in lung over-distention injury (Vlahakis and Hubmayr 2005). Neutrophils play a prominent role in acute lung injury and their activation by injurious mechanical ventilation strategies continues to be an area of active investigation, with stretch induced stiffening of neutrophils and signaling through c-Jun N-terminal kinase (Choudhury et al. 2004; Li et al. 2004) both implicated in neutrophil margination and activation in the lung microcirculation. The observation that ventilation may result in profoundly different outcomes in neo-natal versus adult populations has led to the development of comparative animal ventilation models which should help to uncover the developmental basis for differential responses to lung distention (Copland et al. 2004; Kornecki et al. 2005). While hypothesis-driven approaches provide mechanistic dissection of ventilation-induced biochemical signaling, discovery based approaches have also been implemented to survey the landscape of transcriptional events initiated by stretch. Microarray analyses highlight genomic scale events, transcriptional programs and candidate genes evoked by the ventilation in various model systems (Grigoryev et al. 2004; Altemeier et al. 2005; Ma et al. 2005; Dolinay et al. 2006; Gharib et al. 2006; Simon et al. 2006; Wurfel 2007; dos Santos et al. 2008). Ultimately, the challenge will be to reverse engineer the mechanobiological pathways underlying these transcriptional programs, and develop strategies based on this knowledge to avoid or attenuate adverse responses to mechanical ventilation.

Stretching lung cells

In parallel with animal models of ventilation, cell culture approaches are being widely exploited to accelerate discovery and characterization of mechanical signaling events in lung cells. While limited in their capacity to recapitulate in vivo biology and the complex intercellular interactions that are present in the lung, these models provide enhanced control of the mechanical and biochemical environment, and offer ready opportunities to interrogate specific cellular and molecular events modulated by mechanical stimuli.

Many of the cellular mechanobiology studies relevant to the lung focus on the epithelium, which covers the vast surface area of the lung, and thus represents a potent source for mechanical regulation. Not surprisingly, studies of distal lung epithelium largely parallel whole lung studies with interrelated emphases on development and differentiation, growth responses, and injury mechanisms. Studies of fetal lung cells have identified a vast array of signaling responses to stretch (Copland and Post 2007), as well as secretion of paracrine mediators such as prostanoids (Copland et al. 2006) and serotonin (Pan et al. 2006). Confirming the stimulatory effects of stretch on accelerated lung maturation and cellular differentiation, cell culture studies demonstrate the potent effects of stretch on fetal type II epithelial differentiation, with contributions from EGFR (Sanchez-Esteban et al. 2004), integrins β1, α6, and α3 (Sanchez-Esteban et al. 2006), and cAMP-PKA signaling (Wang et al. 2006). Global microarray analysis of fetal type II epithelium exposed to stretch demonstrated enhanced expression of a variety of genes, including the amiloride-sensitive epithelial sodium channel gene (Scnn1a), suggesting a role for stretch in preparing the developing epithelium for the transition from net

secretion to absorption at birth (Wang et al. 2006). Together these studies provide testable new hypotheses for critical regulatory nodes in mechanical regulation of lung development.

In cells representative of those in the mature lung, stretch has been shown to exert potent effects on growth, structure, homeostasis and differentiated function. Cyclic stretch drives the production of reactive oxygen species (ROS) in distal lung epithelial cells (Chapman et al. 2005) necessary for stretch-induced cellular proliferation (Chess et al. 2005). The growth regulation of epithelial cells by stretch also requires contributions from Src, FAK, and ERK, emphasizing the complex interplay of regulatory signals governing cellular proliferation in response to mechanical stimulation (Chaturvedi et al. 2007). A novel dystroglycan-dependent mechanotransduction response has been observed in stretched alveolar cells (Jones et al. 2005), and contributes to activation of AMP kinase and ERK (Jones et al. 2005; Budinger et al. 2008). Stretch also leads to remodeling of the epithelial intermediate filament network (Felder et al. 2008) and actin cytoskeleton (Papaiahgari et al. 2007), and calcium-dependent fusion of lamellar bodies with the cell membrane (Frick et al. 2004). Lamellar bodies are the densely packed structures used by cells to store and deliver the phospholipid components of pulmonary surfactant. Interestingly, mixed cultures of type I and type II cells respond to stretch with greater phospholipid secretion than type II cells alone, implicating type I cells as primary mechanosensors which stimulate secretion in neighboring type II cells though extracellular ATP signaling (Patel et al. 2005).

As in the intact lung, not all effects of stretch are beneficial or benign for distal lung epithelial cells. Cyclic stretch causes an acidification response that promotes bacterial growth (Pugin et al. 2008), impairs the barrier function of epithelial monolayers (Cavanaugh et al. 2006), and leads to cell death and release of cytokines that play important roles in ventilator-induced lung injury (Hammerschmidt et al. 2004; Hammerschmidt et al. 2005; Hammerschmidt et al. 2007). Cell culture models also recapitulate the observation that moderate stretch alone is less provocative of cellular responses than is stretch in the presence of an infectious agent (LPS) or inflammatory cytokine (TNF-alpha) (dos Santos et al. 2004). Intriguingly, there is one example of using cell culture models to show that the epithelium can be treated to enhance its resistance to the negative effects of stretch, with compelling evidence that IL-10 has protective effects worthy of follow-on study in animal models (Lee et al. 2008). Similarly, experimental and computational approaches have been employed to study stretch-induced increase in Na-K-ATPase pumping activity (Fisher and Margulies 2007), which could be a target to improve fluid clearance from airspaces in acute lung injury.

For the proximal airways, air-liquid interface cultures of primary bronchial epithelium faithfully recapitulate the differentiated character of this tissue, and have been used to elucidate both ATP- and EGFR-dependent modes of epithelial mechanotransduction (Tschumperlin et al. 2004; Kojic et al. 2006; Button et al. 2007). The EGFR-dependent response is evoked by compressive stress shrinking the lateral intercellular space (Fig. 3A-B), and has been further linked to positive feedback signal amplification and activation of the plasminogen family of enzymes that exert broad control over matrix remodeling pathways (Chu et al. 2005; Chu et al. 2006). Mechanotransduction of chronic intermittent compressive stress (Fig. 3C) also enhances expression of mucin protein (Park and Tschumperlin 2009), suggesting a causal link between mechanical perturbations in the airways and excessive mucus production that contributes to airway obstruction. Further effort has led to the development of co-culture models which incorporate differentiated epithelium adjacent to cell-populated collagen matrices, allowing for cell-cell communication in configurations approximating the native airway wall (Choe et al. 2006). These systems demonstrate an integrated tissue remodeling response to mechanical stress that resembles many of the features of asthmatic airway remodeling (Swartz et al. 2001).

Opportunities and Challenges

The new tools and methods being deployed for mechanobiology investigation in the lung are accelerating the pace of discovery, and creating opportunities for breakthroughs. While the challenges are many, the field appears poised for tackle longstanding questions. Furthermore, the chance to translate basic understanding into clinical practice and therapies is real and closer than ever before. Below we present several thematic areas that, from our perspective, appear ripe for discovery, synthesis, and innovation.

Throughout the text the diverse and profound effects of lung distention in vivo, and stretch in vitro have been emphasized. Unresolved to this day is the paradoxical observation that stretch is necessary for lung growth and regeneration, but also capable of causing or exacerbating injury in the context of mechanical ventilation. While this paradox might be dismissed as an issue of degree, with small distention promoting growth, and large distention causing injury, several lines of evidence indicate that the situation is more complex. Moderate to large lung distention, in the absence of preexisting injury or infection, can be quite well tolerated (Hsia 2004). In contrast, even modest degrees of lung distention can cause or amplify injury when applied to lungs with local or systemic inflammation (Altemeier et al. 2004; Altemeier et al. 2005). The interaction between the immune system, the existing soluble milieu, and the cellular responses to stretch would appear to constitute a highly complex, but extraordinarily important intersection. If critical mediators or pathways could be identified to shift cellular stretch responses from those associated with injury and inflammatory signaling toward those responses associated with growth and regeneration, the implications for both mechanical ventilation and lung regeneration would be profound.

Similarly, nascent efforts to engineer lung tissue (Hoganson et al. 2008; Nichols and Cortiella 2008; Zani et al. 2008), or develop scaffolds for lung tissue regeneration would appear natural beneficiaries of enhanced understanding of the key pathways that promote growth and regeneration responses to lung distention. Here the investigation of lung development, and the differing responses of neonatal and mature lungs to mechanical perturbations could be employed to uncover critical pathways selectively activated in lung growth (Copland et al. 2004; Kornecki et al. 2005). As knowledge of progenitor cell function in the lung advances, the effects of the mechanical environment on these cells will also need to be elucidated. For instance, it will be interesting to define whether the mechanical environment is one of the characteristics that defines niches for progenitor cells, or plays any role in commitment of progenitor cells to various lung-specific lineages.

While stretch has been, and will continue to be a focal point for mechanobiological investigation in the lung, the role of stiffness appears poised for increased recognition. The lung parenchyma is a highly compliant tissue, and prominent diseases such as pulmonary fibrosis, emphysema, and asthmatic airway remodeling alter lung tissue compliance. The role that stiffness plays in initiating, amplifying, or prolonging these disease processes represents fertile but as yet unexplored territory. Moreover, the already discussed in vitro effects of stretch may need to be re-evaluated with regards to stiffness – it is not known if stretching cells on soft, physiologic stiffness substrates, as opposed to the much stiffer elastic substrates currently employed, will alter cell responses to stretch. In the lung, the amount of tissue stretch is linked to the local and global tissue stiffness, thus as disease processes remodel the lung the tonic and cyclic levels of local distention will simultaneously change. The development of in vitro models capable of simultaneously modulating stretch and stiffness will be needed to explore the intersection of these key aspects of the mechanical environment.

Finally, the search for mechanisms of mechanotransduction in the lung, which has been quite successful over the past several years, has led to an unexpected question: what cellular

processes and signaling pathways are unaffected by stretch (and perhaps stiffness)? While clearly there are cell-specific and stimulus specific mechanotransduction responses, it is also increasingly clear that mechanical events can have wide-ranging and potent effects across a variety of pathways and cell types (Trepat et al. 2007). We suggest that the field could benefit from applying integrative and systems type approaches (Janes et al. 2005; Miller-Jensen et al. 2007; Simpson et al. 2008) to dissect critical mechanoregulated events in the lung and lung cells. Such an approach appears especially appealing in light of the diversity of responses known to occur downstream from lung distention, and the divergent physiological responses that can emerge when similar stimuli are applied in different contexts. The application of genomics, proteomics, and systems biology tools and approaches will be increasingly necessary as we move toward a more integrated understanding of mechanobiolgical processes in lung health and disease.

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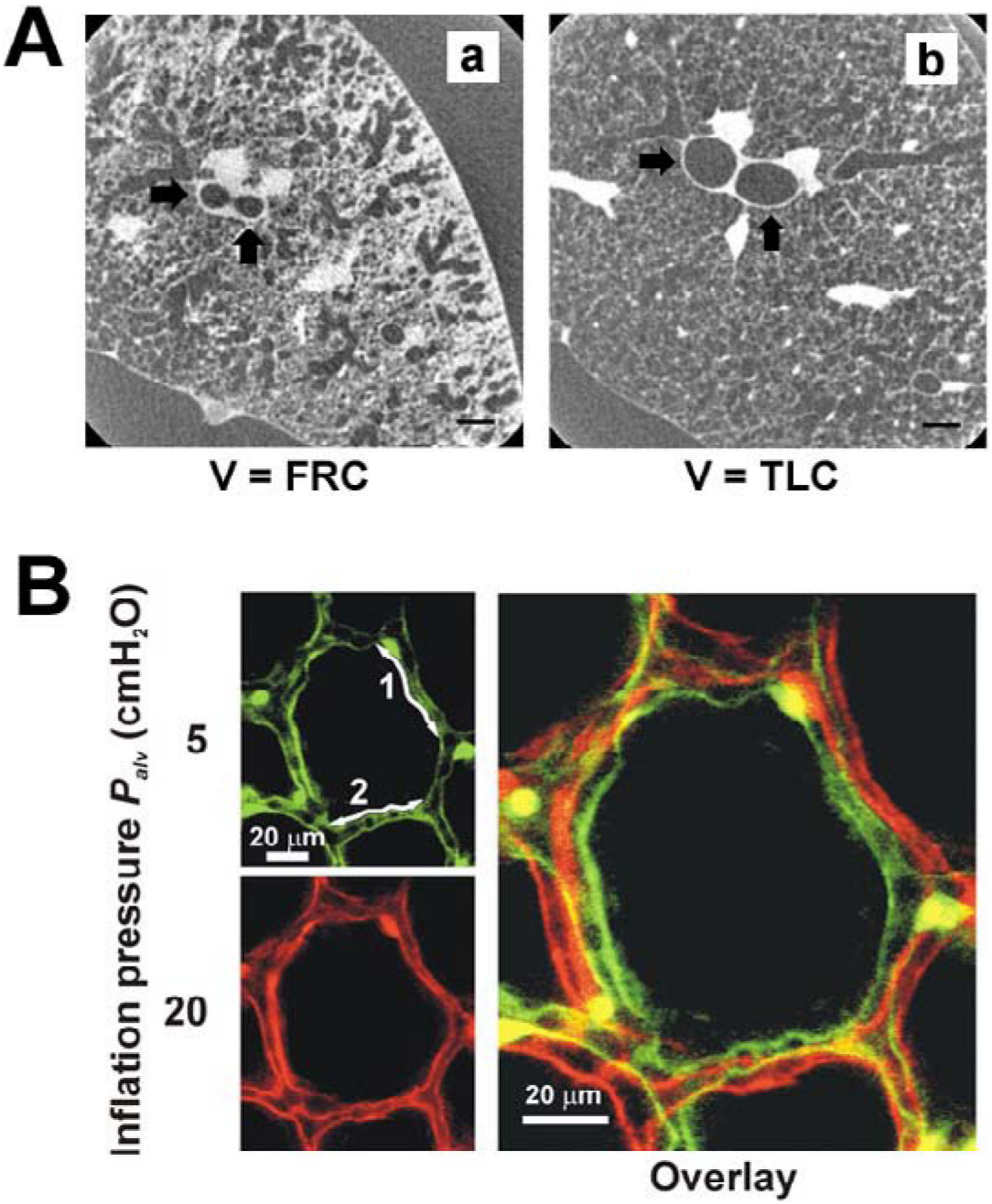

Figure 1.

(A) Micro-CT images of rat lung airways at inflation volumes of (a) functional residual capacity (FRC) and (b) total lung capacity (TLC). Same-direction arrows indicate the same airways. Scale bar, 500 μm. Adapted with permission from (Sera et al. 2004). (B) The same rat lung alveolus imaged with intravital microscopy at transpulmonary inflation pressures of 5 cmH2O (green pseudocolor) and 20 cmH2O (red pseudocolor). Numbers in baseline image label two perimeter segments. An overlay of the images demonstrates inflation-induced alveolar expansion, which increased total alveolar perimeter length, *L* and alveolar diameter, *D* by 13 and 15%, respectively. Adapted with permission from (Perlman and Bhattacharya 2007).

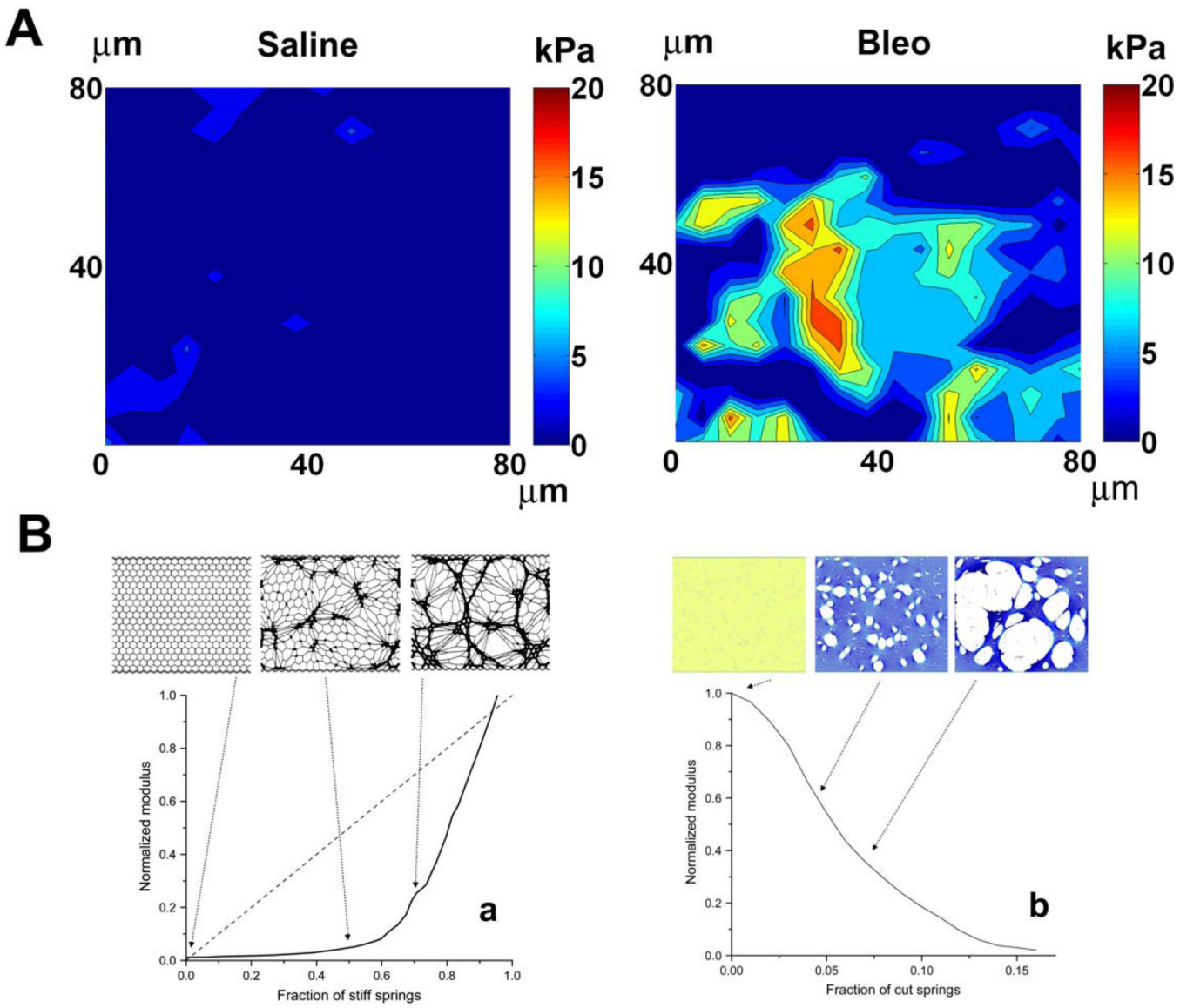

Figure 2.

(A) Representative stiffness maps of normal and fibrotic (14 days post bleomycin treatment) mouse lung parenchyma. Colorbar indicates shear modulus. AFM force-indentation profiles were acquired in a 16×16 sample grid separated by 5 μm spatially covering 80×80 μm area. Shear modulus at each point on the grid was calculated from fitting force-indentation data using a Hertz sphere model and resulting shear modulus data were plotted in a contour map (unpublished data). (B) Simulation of the progression of pulmonary fibrosis (a) and emphysema (b) based on percolation of sequential alveolar wall stiffening or rupture. (a) The curve shows the bulk modulus of the elastic network versus the fraction of springs randomly stiffened by a factor of 100. If all the spring constants were uniformly stiffened in a gradual manner from the baseline value of 1 to 100, the modulus would follow the dashed diagonal line. Top: Network configurations obtained when 0, 50, and 67% of the springs have been stiffened. (b) The curve shows the bulk modulus of the elastic network versus the fraction of springs cut on the basis of the amount of tension they carry. Top: Network configurations obtained at three points along this process. The stresses in the individual springs are indicated

by color coding, with yellow indicating high stress and decreasing stress corresponding to progressively darker shades of blue. Adapted with permission from (Bates et al 2007).

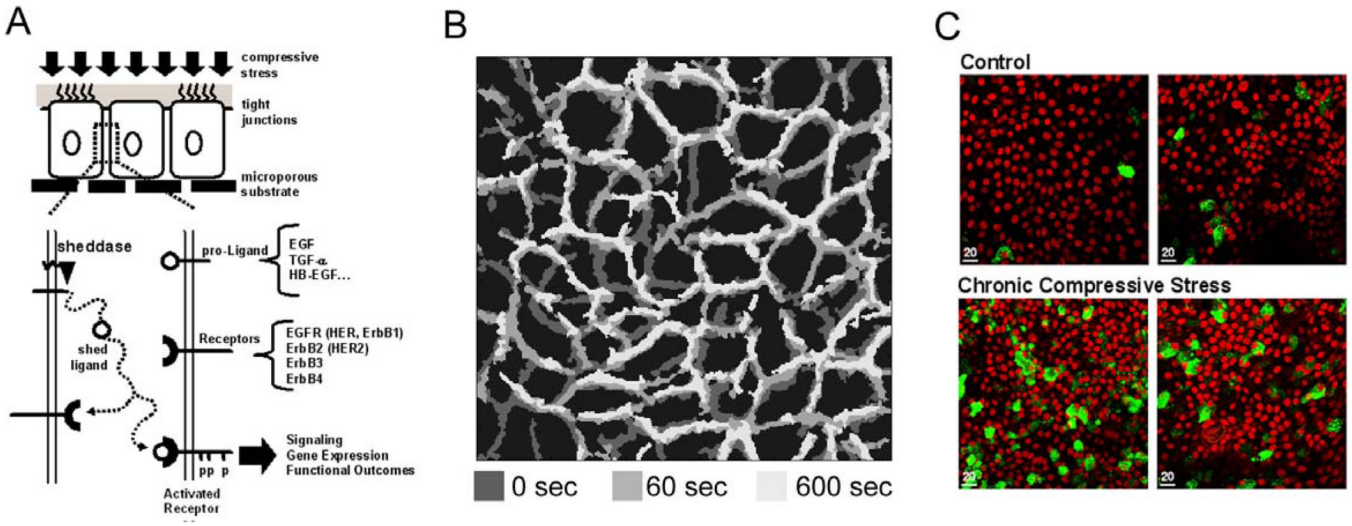

Figure 3.

(A) Schematic of bronchial epithelial cells cultured at air-liquid interface on a microporous substrate. The lateral cellular surfaces express pro-ligands of the EGF family and their cognate EGFR receptors, forming a local autocrine circuit. (B) Compressive stress (apical to basal transcellular pressure gradient) shrinks the lateral intercellular space between neighboring bronchial epithelial cells, visualized by two-photon imaging of extracellular fluorescent dextran. Sequential images at baseline (0 seconds), 60 and 600 seconds after initiation of continuous compressive stress illustrate the gradual decline in intercellular gap distance. (C) Chronic intermittent exposure to compressive stress daily for 14 days enhances expression of a mucus secretory phenotype, visualized by immunofluorescent staining of MUC5AC (green). Nuclear counterstain is shown in red.