Desmin modulates lung elastic recoil and airway responsiveness

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1Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas; 2Division of Cell Biology, Center of Basic Research, Academy of Athens, Athens, Greece; and 3Department of Medicine, Baylor College of Medicine, Houston, Texas

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Shardonofsky, Felix R., Yassemi Capetanaki, and Aladin M. Boriek. Desmin modulates lung elastic recoil and airway responsiveness. Am J Physiol Lung Cell Mol Physiol 290: L890–L896, 2006. First published December 30, 2005; doi:10.1152/ajplung.00397.2005.—Desmin is a structural protein that is expressed in smooth muscle cells of both airways and alveolar ducts. Therefore, desmin could be well situated to participate in passive and contractile force transmission in the lung. We hypothesized that desmin modulates lung compliance, lung recoil pressure, and airway contractile response. To test this hypothesis, respiratory system complex impedance ($Z_{in,rs}$) at different positive end-expiratory pressure (PEEP) levels and quasi-static pressure-volume data were obtained in desmin-null and wild-type mice at baseline and during methacholine administration. Airways and lung tissue properties were partitioned by fitting $Z_{in,rs}$ to a constant-phase model. Relative to controls, desmin-null mice showed 1) lower values for lung stiffness and recoil pressure at baseline and induced airway constriction, 2) greater negative PEEP dependence of $H$ and airway resistance under baseline conditions and cholinergic stimulation, and 3) airway hyperresponsiveness. These results demonstrate that desmin is a load-bearing protein that stiffens the airways and consequently the lung and modulates airway contractile response.

Compliance; hysteresis; airway resistance

THE MACROMECHANICAL PROPERTIES of the lung are determined by a complex interaction among load-bearing components of lung tissue, i.e., collagen, elastin, and proteoglycans, the alveolar air-liquid interface, interstitial cells, as well as conducting airways and vessels embedded in lung tissue (1, 7, 16, 32, 34). Experimental studies have shown that in the absence of contractile cell stimulation, lung mechanical properties largely reflect those of the connective tissue fiber skeleton and surface film (34). In addition, the state of activation of contractile interstitial and airway cells affects the macromechanical behavior of the lung, as lung stiffness ($H$), energy dissipative behavior, and hysteresis ($\eta$) have been reported to increase or decrease in response to the administration of contractile or relaxant agonists, respectively (6). However, there is no information regarding the mechanical contribution of the cytoskeleton of airway smooth muscle (ASM) cells to the overall mechanical behavior of the lung. Desmin is a cytoskeletal protein that has been shown to contribute to mechanical properties of skeletal (3, 22), cardiac (2, 17, 18), and visceral smooth muscles (27, 31) as a result of its involvement in force transmission (27, 31), maintenance of cell alignment (20, 22), positioning (20, 22), distribution, function of mitochondria (19, 22), and mechanotransduction (14, 20). Because desmin is expressed in smooth muscle cells located in airways (8, 21) and alveolar ducts (5, 13, 33), we hypothesized that desmin modulates lung compliance, lung elastic recoil pressure, and airway contractile response. We tested this hypothesis by determining the dynamic and quasi-static properties of the lung in vivo in transgenic mice in which the gene encoding for desmin was inactivated and in wild-type counterparts. Our results show that desmin is an intracellular load-bearing protein that influences airway compliance, lung recoil, and airway contractile responsiveness.

METHODS

Respiratory system complex input impedance ($Z_{in,rs}$) at different levels of positive end-expiratory pressure (PEEP) and quasi-static transrespiratory pressure-volume ($Pst,rs-V$) data obtained under both baseline conditions and methacholine-induced ASM activation in 129SV desmin-null mice (desmin−/−) were compared with those obtained in 129SV wild-type counterparts (desmin+/+) under identical experimental protocols. All experiments were approved by the Animal Research Ethics Board of Baylor College of Medicine.

Animal preparation. Experiments were performed on 129SV desmin−/− mice ($n = 11$) and 129SV desmin+/+ mice ($n = 12$) weighing 21 ± 1 g (means ± SD) and 25 ± 1 g ($P < 0.001$), respectively. Mutant mice had been developed by Milner et al. (17) by homologous recombination. The murine colonies were raised and kept at a Baylor College of Medicine animal facility under standard conditions of temperature and light and dark periods, while mice were fed chow and water at libitum. Anesthesia was induced by intraperitoneal (ip) injections of 0.5–0.7 mL/kg of a rodent anesthetic compound containing xylazine (8.6 mL/kg), acepromazine (1.4 mL/kg), and ketamine (42.8 mL/kg) (Center for Comparative Medicine, Baylor College of Medicine). Thirty minutes after the administration of the first dose of anesthetic compound, a second dose of 0.25 mL/kg ip was given to each mouse to ensure proper level of anesthesia for the entire duration of the study, which was ~50 min. When motor responses to nociceptive stimuli and corneal reflex were abolished, a 27 × 3/8 butterfly needle (Abbott, Chicago, IL) was inserted into a tail vein for drug administration, and a 6-mm-long, 22-gauge over-the-needle catheter (Abbocath-T, Venisystems) was inserted into the trachea via a tracheotomy performed just beneath the cricoid cartilage. The tracheal cannula was properly secured with surgical thread and then connected to a computer-driven small-animal ventilator (Flexivent; SCIREQ, Montreal, Canada). Mice were ventilated in the supine position with room air, tidal volume of 8 mL/kg delivered at a rate of 3 Hz and a PEEP of 2 cmH2O. Once bilateral chest wall expansion was observed, muscle paralysis was induced by an injection of ~0.8 mg/kg ip of pancuronium bromide (Abbott) to ensure that data were collected under passive mechanical conditions. Care was taken to avoid air leaks. At the end of the experiments, mice were killed by exsanguination.

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Measurement of Zin,rs. Zin,rs spectra and Pst,rs-V data were obtained with the Flexivent system (24). Cylinder pressure and piston displacement signals were low-pass filtered at 30 Hz and sampled at 256 Hz. Before each mouse was connected to the mechanical ventilator, pressure and piston displacement calibration data were collected to compute the elastance of the measuring equipment and airflow resistance of the tracheal cannula, which were used to correct the respiratory mechanics data (24). To standardize the volume history of the respiratory system, the lungs were inflated to a transrespiratory pressure (Prs) of ~30 cmH\textsubscript{2}O 1 min before data sampling. To obtain Zin,rs spectra, mechanical ventilation was discontinued for 9 s, during which the expiratory valve of the respirator remained open for 1 s, allowing the lungs to expire passively down to the functional residual capacity (FRC) determined by the PEEP level. The expiratory valve was then closed, and an 8-s volume perturbation was delivered to the airway opening ventilator, regular mechanical ventilation being resumed immediately thereafter. The 8-s signal that drove the ventilator’s piston for measurements of Zin,rs was composed of 19 sinusoids that had mutually prime frequencies from 0.5 to 19.75 Hz and amplitudes that decreased hyperbolically with frequency, so that the values for power spectrum of flow were similar in the prescribed frequency range. The phases of the sinusoids were chosen to minimize the peak-peak amplitude of the volume perturbation signal, which was ~30% of the tidal volume used during mechanical ventilation. We calculated Zin,rs by dividing the fast Fourier transform of Prs by the transform of flow (dV/dt) at each frequency and dividing the result by \(-j\pi f\). Under baseline conditions and during methacholine-induced constriction, Zin,rs data were obtained at 0, 2, and 8 cmH\textsubscript{2}O of PEEP.

Airway and respiratory tissue properties were partitioned by fitting Zin,rs to a constant-phase model of the respiratory system that features a frequency-independent resistance [airway resistance (Raw)] and inertance [airway inertance (law)] in series with a constant-phase tissue compartment containing tissue damping (G) and H parameters that reflect the viscous dissipation of energy and energy storage in the respiratory tissues, respectively (9):

\[
\text{Zin,rs} = \text{Raw} + j\alpha_{\text{law}} + (G - jH)/2\pi f^{\alpha}
\]

where \(j\) is the imaginary unit, \(f\) is frequency in Hz, and \(\alpha = (2/\pi)\arctan(H/G)\). Zin,rs, coherence function, and constant-phase model parameters were computed with the Flexivent software. The values for law were negligible and are not reported.

Measurement of Pst,rs-V data. To obtain Pst,rs-V data, the volume history was standardized and mice were kept at 0 cmH\textsubscript{2}O of PEEP for 1 min. Then, regular ventilation was stopped for 16 s during which alveolar pressure was allowed to equilibrate to atmospheric pressure for 1 s and the lung volume was raised to ~15 ml/kg and decreased back to FRC in a stepwise fashion. At each volume step, Pst,rs was measured at the end of a 100-ms pause. Immediately after data collection was completed, regular mechanical ventilation was restarted. The nonlinear relationships of the Pst,rs-V data were fit to a collection was completed, regular mechanical ventilation was re-started. The nonlinear relationships of the Pst,rs-V data were fit to a

Assessment of airway responsiveness to cholinergic stimulation. After baseline measurements were obtained, mice were intravenously infused normal saline solution (vehicle) followed by a solution containing 300 \(\mu\)g/ml of acetyl-\(\beta\)-methylcholine chloride (methacholine; Sigma Chemical, St. Louis, MO) by means of a syringe infusion pump (Raze Scientific Instruments, Stamford, CT). The methacholine infusion was begun at 0.016 ml/min, the rate being progressively doubled to a maximum of 0.272 ml/min. Each methacholine dose was infused for ~7 min, during which Zin,rs were obtained at PEEP levels of 0, 2, and 8 cmH\textsubscript{2}O, whereas Pst,rs-V data were collected at 0 cmH\textsubscript{2}O of PEEP. To assess the degree of airway responsiveness, Raw vs. log\textsubscript{2} methacholine dose relationships were constructed. The slope of the quasi-linear portion of the Raw-log\textsubscript{2} methacholine dose relationship was computed by multiple linear regression analysis, and the highest value for Raw during methacholine infusion was taken as maximum airway response.

Statistical analysis. Results are reported as means ± SE. Comparisons between experimental and control mice were performed by two-tailed, nonpaired \(t\)-test. The effects of PEEP on respiratory mechanics in each group were analyzed by analysis of variance and Bonferroni test. A \(P\) value <0.05 was considered statistically significant. The SPSS 9.0 software package (SPSS, Chicago, IL) was used to perform the statistical analysis.

RESULTS

Desmin increases lung stiffness and decreases the hysteretic behavior of the lung in the nonconstricted state. The coefficients describing the dynamic properties of the respiratory system under baseline conditions in both groups of mice are plotted as a function of PEEP in Fig. 1. In wild-type mice, the values for model parameters and their variations with PEEP were similar to those previously reported (28). As evident from Fig. 1, the most striking features associated with a lack of desmin expression were a decreased H normalized for body weight (BW) (Fig. 1C) and an enhanced \(\eta\) (Fig. 1D) at all levels of PEEP studied relative to controls (two-tailed \(t\)-test for \(H\) and \(\eta\) at all PEEP levels: \(P < 0.001\)). On other hand, the magnitudes for Raw (Fig. 1A) and G (Fig. 1B) in mutant mice were not statistically different from those obtained in wild-type mice. An analysis of variance showed that whereas G was independent of PEEP, Raw, \(H\), and \(\eta\) varied significantly with increasing PEEP in all mice studied (Figs. 1), the magnitudes of the PEEP-induced variations in Raw, \(H\), and \(\eta\) being significantly higher in desmin\(-/-\) mice than in wild-type mice (Fig. 2).

Compared with control mice, the average Pst,rs-V characteristic in desmin\(-/-\) animals showed a marked curvilinearity as the rate of rise of Pst,rs with increasing volume was lower in desmin\(-/-\) mice than in wild-type mice (Fig. 3A). The values for Pst,rs\(_{10}\) were 4.58 ± 0.13 cmH\textsubscript{2}O and 6.79 ± 0.21 cmH\textsubscript{2}O for desmin\(-/-\) and desmin\(+/+\) mice, respectively (\(P = 0.003\)). These results indicate that desmin filaments are stress-bearing elements in the lung that enhance overall H and diminish lung hysteretic behavior. The increasing disparity in Pst,rs between desmin-deficient and wild-type mice as lung volume is enhanced, and the differences in PEEP-related changes in \(H\) and Raw between the two groups of mice imply that desmin filaments become mechanically stressed at volumes above FRC. A reduced PEEP-related variation in Raw in wild-type mice relative to that in desmin\(-/-\) mice suggests that desmin could contribute to increase the airway circumferential stiffness.

Desmin enhances airway responsiveness, airway elastance, and active lung recoil. The average Raw-methacholine dose relationships obtained in the two groups of mice are shown in Fig. 4. For desmin\(-/-\) and desmin\(+/+\) mice, the values for sensitivity of Raw vs. methacholine dose relationship were 0.98 ± 0.13 cmH\textsubscript{2}O·ml\textsuperscript{-1}·s·(log\textsubscript{10}·kg·kg\textsuperscript{-1}·min\textsuperscript{-1})\textsuperscript{-1} and 1.47 ± 0.08 cmH\textsubscript{2}O·ml\textsuperscript{-1}·s·(log\textsubscript{10}·kg·kg\textsuperscript{-1}·min\textsuperscript{-1})\textsuperscript{-1} (\(P = 0.002\)), respectively, and those for maximal constractor response were 3.51 ± 0.35 cmH\textsubscript{2}O·ml\textsuperscript{-1}·s and 4.67 ± 0.24 cmH\textsubscript{2}O·ml\textsuperscript{-1}·s (\(P = 0.002\)), respectively. These results indicate that relative to wild-type mice, desmin\(-/-\) mice exhibit airway hyporesponsiveness to cholinergic stimulation.
To further investigate the role of desmin under conditions of ASM activation, respiratory mechanics were examined in both groups of mice when they experienced similar degrees of induced airway narrowing at 0 cmH2O of PEEP. This was achieved in desmin−/− and desmin+/+ mice during methacholine administration at log2 doses of 11.9 μg·kg−1·min−1 and log2 9.7 μg·kg−1·min−1, respectively (Fig. 4). The values for H corrected for BW during cholinergic stimulation were lower in desmin−/− mice than in controls (P<0.001) (Fig. 5C), whereas the magnitudes of G and η in the two groups of mice were not statistically different from each other (Fig. 5, B and D). The magnitude of Raw decreased with increasing PEEP in all mice. Notably, PEEP-induced Raw reductions were greater in desmin−/− than in controls (P<0.01) (Fig. 6, A and B), suggesting that a lack of desmin expression was associated with an increase in airway compliance under conditions of

Fig. 1. Effects of desmin expression on respiratory system mechanics in the nonconstricted state. Average ± SE values for airway resistance (Raw), tissue damping (G), tissue stiffness (H) corrected for body weight (BW), and hysteresivity (η) obtained in wild-type (desmin+/+, n = 11) and desmin-null (desmin−/−) mice (n = 11) are shown as a function of PEEP level in A, B, C, and D, respectively. PEEP, positive end-expiratory pressure. *, **, ***P<0.05, <0.01, and <0.001, respectively, obtained by nonpaired t-test.

Fig. 2. Lack of desmin expression enhanced the negative PEEP dependence of Raw and H. Percentage changes of Raw, H, G, and η obtained in desmin−/− (n = 11) and desmin+/+ (n = 11) mice in response to increases in PEEP from 0 to 2 cmH2O and from 0 to 8 cmH2O are depicted in A and B, respectively. Data are means ± SE. ** and ***P<0.01, and P<0.001, respectively, obtained by nonpaired t-test.
ASM activation. In addition, in desmin−/− mice but not in controls, PEEP elevations produced significant and matched reductions in G (F = 13.00, P < 0.001) and H (F = 60.61, P < 0.001) so that η remained independent of PEEP (Fig. 5D). This was in contrast to the marked PEEP dependence of η shown by desmin−/+ under baseline conditions.

The average Pst,rs−V relationships obtained at similar levels of induced airway narrowing (Fig. 3B) were qualitatively similar to those in the nonconstricted state (Fig. 3A), i.e., increases in lung volume above FRC produced smaller increases in Pst,rs in desmin−/− than in controls, the values for Pst,rs10 being 6.11 ± 0.27 cmH2O and 10.62 ± 1.18 cmH2O (P < 0.01), respectively. The difference between Pst,rs10 obtained during induced ASM activation and baseline conditions reflects the contribution of the active component of lung recoil, which amounted to 3.82 ± 1.11 cmH2O and 1.53 ± 0.16 cmH2O for desmin+/+ and desmin−/− mice (P = 0.046), respectively. Together, these results demonstrate that desmin contributes to physiological airway contractile response and active lung recoil and suggest that desmin is an important intracellular stress-bearing element that participates in the transmission of active mechanical stresses in the lung.

DISCUSSION

This study shows that ablation of desmin expression in mice alters lung elasticity and airway responsiveness. Compared with wild-type mice, desmin−/− mice exhibited 1) reduced H and recoil pressure (Pst,rs), 2) greater negative PEEP dependence of H and Raw, 3) enhanced hysteretic behavior (η), and 4) airway hyporesponsiveness to cholinergic stimulation.

A lack of desmin expression has been shown to alter the passive mechanical properties of the diaphragm (3), and hence, it may alter those of the chest wall. In mice, however, the contribution of chest wall mechanical properties to respiratory system mechanics has been shown to be negligible (28), suggesting that the differences in the mechanical properties of the respiratory system between the two groups of mice studied are due to differences in the mechanical properties of the lung.

Effects of desmin on lung mechanics in the absence of contractile cell stimulation. In tissues containing smooth muscle cells expressing desmin such as bladder, vas deferens (27), and resistance arteries (31), inactivation of desmin expression is associated with reductions in the magnitudes of passive and active tissue stresses relative to controls. This was not accounted for by disturbances in the structure of smooth muscle on electron microscopy, amount of contractile proteins, cell activation, or electromechanical coupling (27). On the basis of these data and the fact that desmin filaments in smooth muscle cells are concentrated in dense bodies, i.e., structures equivalent to Z-disks in sarcomeric cells (5, 20), Sjuve et al. (27) have argued that desmin filaments contribute to stabilize the contractile units and participate in stress transmission between contractile units and anchorage sites linking to the extracellular matrix through the cell membrane as well as in the parallel coupling of sarcomere equivalents. In line with the aforementioned data obtained in bladder (27), vas deferens (27), and resistance arteries (31) in desmin−/− mice, the reductions in H, Pst,rs, and airway responsiveness to methacholine observed in our desmin−/− mice relative to wild-type counterparts indicate that in the lung, desmin behaves as a load-bearing element that contributes to the transmission of passive and active mechanical stresses. The differences in PEEP dependence of both H and Raw and the increasing discrepancy of Pst,rs as lung volume rose between desmin−/− and control mice indicate that desmin filaments are mechanically loaded at lung volumes above FRC.
In the lung, desmin is expressed by smooth muscle cells located in the walls of conducting airways (8, 21) and alveolar ducts (5, 13, 33). In addition, myofibroblasts normally encountered in alveolar septa have been shown to express desmin in some species such as rodent and swine but not in human beings (13). According to Yuan and colleagues (34), the contribution of nonactivated interstitial myofibroblasts and smooth muscle cells in alveolar ducts to the macromechanical properties of the lung appears to be negligible. On the other hand, the differences in PEEP dependence of Raw between desmin−/− mice and control mice under both baseline conditions (Figs. 1 and 2) and similar levels of induced airway narrowing (Figs. 5 and 6) strongly suggest that desmin increases the airway circumferential stiffness, a notion buttressed by the putative mechanical functions of desmin in smooth muscle cells and the elevated density of these cells in the airway wall. Alternatively, an increased negative PEEP dependence of Raw in desmin−/− mice could reflect a greater degree of airway-parenchymal

Fig. 5. Effects of desmin expression on PEEP dependence of respiratory system mechanics during similar levels of induced airway narrowing at 0 cmH2O of PEEP. Data were obtained in desmin+/+ (n = 11) and desmin−/− mice (n = 12) at similar levels of methacholine-induced airway narrowing at PEEP = 0 cmH2O (see text). Average ± SE values for Raw, G, H corrected for BW, and hysteresivity (η) are shown as a function of PEEP in A, B, C, and D, respectively. *, **, and ***P < 0.05, P < 0.01, and P < 0.001, respectively, obtained by nonpaired t-test.

Fig. 6. Effects of desmin expression on PEEP-dependent variations of respiratory mechanics during similar levels of cholinergic stimulation. Data were obtained in wild-type (n = 11) and desmin−/− mice (n = 12) during iv administration of average log2 methacholine doses of 9.73 and 11.9 μg·kg−1·min−1, respectively (See Fig 4). Percentage change of Raw, H, G, and η in response to increases in PEEP from 0 to 2 cmH2O and from 0 to 8 cmH2O are depicted in A and B, respectively. Data are means ± SE. ** and ***P < 0.01 and P < 0.001, respectively, obtained by nonpaired t-test.
interdependence relative to controls (15). It can be argued that desmin is not expressed in alveolar septa during and after alveolar development (4), and therefore, ablation of desmin’s expression would not be expected to affect the airway-parenchymal interdependence. However, gene suppression in germinal cells might have brought about unanticipated compensatory variations in protein expression and lung structure; to the best of our knowledge, there are no data available in the literature to elucidate this matter.

The elastic properties of the airways influence the overall elastic properties of the lung as a result of the coupling between the mechanical properties in the circumferential and axial directions of the airways. Whereas passive lengthening of relaxed excised bronchi produces a compressive stress that decreases airway diameter (25), length and diameter of bronchi “in situ” augment in proportion with the cube root of lung volume (11) as a result of increases in the magnitudes of both airway transmural pressure and forces of airway-parenchymal interdependence as lung volume rises (15). Therefore, the enhanced circumferential airway stiffness as a result of desmin’s being mechanically stressed would raise H and recoil. Desmin could also affect the axial mechanical properties of the airways. In skeletal myocytes, desmin filaments are oriented in both the transverse and longitudinal planes, linking Z-disks in series in a single myofibril as well as adjacent myofibrils arranged in parallel (23, 30). For the diaphragm, desmin could also affect the axial mechanical properties in smooth muscle cells, the role of desmin filaments in ASM cells, which are largely circumferentially arranged in the airway wall, exhibited an organization similar to that in the diaphragm, desmin would increase the magnitude of axial airway stiffness and, therefore, would raise H and lung elastic recoil because a proportion of the work of the mechanical properties in the overall elastic behavior of the lung under both baseline conditions and induced airway constriction.

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Similar (27, 31).

Depletion of active mechanical stress in smooth muscle cells, the role of desmin filaments in ASM cells, which are largely circumferentially arranged in the airway wall, exhibited an organization similar to that in the diaphragm, desmin would increase the magnitude of axial airway stiffness and, therefore, would raise H and lung elastic recoil because a proportion of the work of expanding the lung is required to lengthen the airways (10, 12).

The hysteretic behavior of the overall lung was characterized in terms of η, i.e., the ratio of dissipated (G) to stored (H) energy over the volume oscillation. In the absence of contractile cell stimulation, the values of η and their variation with PEEP were greater in desmin−/− than wild-type mice. This is in contrast with the stability of η after the lung tissue matrix was altered by digestion of elastin or collagen fibers in lung tissue strips (35) and likely reflects changes in the relationship between energy dissipative and storage mechanisms within smooth muscle cells. Interestingly, we demonstrated that in diaphragm muscle, desmin expression is associated with changes in passive viscoelastic properties and increased viscous dissipation during contractile stimulation (3).

**Effects of desmin on lung mechanical properties during cholinergic stimulation.** During cholinergic stimulation, the airway hyporesponsiveness and enhanced PEEP dependence of H and Raw associated with lack of desmin expression support the notion that desmin filaments participate in the transmission of active mechanical stress in smooth muscle cells, the role of desmin being increasingly important at volumes above FRC. We cannot rule out the possibility that airway hyporesponsiveness resulted from reduced number of ASM cells or decreased cellular myosin content. However, studies on visceral smooth muscle cells have shown that the arterial thickness and myosin-to-actin content ratios in desmin−/− and control mice were similar (27, 31).

During cholinergic stimulation, the values for η that increased above those obtained under baseline conditions were similar in the two groups of mice assessed at similar degrees of airway resistance. This suggests that η was dominated by the acto-myosin interactions in smooth muscle cells (6), the cycling rates between actin and myosin being likely similar and independent of desmin expression.

**Physiological implications.** Whereas it is well established that tissue matrix components including collagen, elastin, and proteoglycans and the gas-liquid interface dominate the macromechanical properties of the lung (1, 7, 16, 32), our data show that intracellular proteins such as desmin, which behaves as a load-bearing element and takes part in the transmission of passive and active mechanical stresses, exerts profound effects on lung elastic behavior, η, and airway responsiveness. These data also emphasize the role of the elastic properties of the airways in the overall elastic behavior of the lung under both baseline conditions and induced airway constriction.

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