Cellular Physiology and Biochemistry

Cell Physiol Biochem 2025;59:884-902
DOI: 10.33594/000000834
Published online: 16 December 2025
Accepted: 4 December 2026

Review

Advances in the Study of Bronchial and Vascular Architecture of Lungs in the Rat's Model: from Morphogenesis to Disease Modelling

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Key Words
Angiogenesis • Bronchial–vascular coupling • Lung morphometry • Rat model • Vascular remodeling

Abstract
Bronchial and vascular architecture in the rat lung forms an interdependent scaffold that balances ventilation with perfusion and adapts to metabolic demand. Development proceeds through coordinated branching programs that couple epithelial growth with vascular patterning while matrix remodeling and epithelial–mesenchymal crosstalk shape airway caliber and capillary alignment. Quantification has moved from classical design-based stereology to organ-scale μCT, optical clearing, and multiscale computational reconstructions that link structure to function. Across disease models, Chronic Obstructive Pulmonary Disease (COPD) and emphysema show distal airspace enlargement with vascular rarefaction, pulmonary hypertension (PH) features medial thickening and arteriolar muscularization, asthma combines epithelial remodeling with angiogenesis, and fibrosis exhibits collagen deposition with capillary regression. Convergent signaling networks integrate these changes, including VEGF and HIF pathways that govern angiogenesis, Notch and Wnt programs that regulate morphogenesis, and oxidative stress with cytokine and microRNA axes that drive vascular remodeling. Translational alignment is strengthened by single-cell and imaging biomarkers that map rat phenotypes to human pathology, while bioengineered platforms and in silico models provide controllable test beds for hypothesis testing. Predictive frameworks for remodeling across development and disease could be provided by standardized pipelines that combine morphometry, mechanics, and molecular profiles.

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Introduction

The bronchial and vascular system of the lung ensures even ventilation and perfusion of the parenchyma [1]. Blood oxygenation occurs in the alveolar-capillary interface pulmonary vascular network, and the airflow is controlled by the bronchial tree [2]. Their interdependence in structure promotes effective gas exchange and adaptation to metabolic needs. The close spatial relationship between airway, vascular, lymphatic, and neural networks has also been demonstrated using high-resolution 3D imaging, highlighting the role of architectural integrity in promoting physiological resilience [3]. The study of both development and disease in mammalian lungs is based upon an understanding of these coupled systems.

The FGF10 FGFR2b signaling pathway is required to form lung airways, which is coordinated by biochemical cues and epithelial dynamics to form the hierarchical branching geometry that characterizes lung geometry [4]. The development of the vascular system occurs concurrently via endothelial-mesenchymal signaling, which guarantees the alignment with the airway tree [5]. Mechanistic theories, such as curvature-feedback through ERK, explain how the length and orientation of branches are regulated to achieve morphogenetic homeostasis, with comparative studies revealing that morphogenetic programs are adjusted to functional demands in different organs [6, 7].

The rat has been found to be a useful intermediate model due to its lung size, vascular structure, and hemodynamic accessibility; it has benefits over mice and retains experimental viability [8]. Postnatal μCT imaging indicates persistent alveolar and acinar remodeling, which allows better evaluation of developmental changes [9]. Its clinical value is highlighted by structural changes in heart failure and pulmonary hypertension [10]. The visualization of airway and vascular architecture is now done at high resolution with advanced μCT protocols and CT-based mapping [11, 12].

The recent innovations in stereology have enhanced the measurement of the lung compartments and have made the heterogeneous lesions to be sampled with precision [13]. The ex vivo lung perfusion is relevant to increase the physiological significance of structural evaluation [14]. Whole lung visualization is now achieved at the micron level using the techniques of tissue-clearing and 3D microscopy [15], and high-resolution histological reconstructions that consider the information about gene expression and spatial organization provide new information about the biological process [16]. All these innovations have transformed structural mapping of the rat lung and made it more useful in developmental and disease modeling.

Even though there are significant improvements, there are still gaps in knowledge. The majority of developmental research is based on mice, and rat data are still scarce, even though they are more physiologically similar to humans [17]. The research on airway or vascular remodeling is frequently studied in isolation from each other as opposed to coordinated structural systems [18]. Perfusion pressures and contrast techniques influence distal vascular accuracy, whereas 3DCT and tissue clearing have enhanced visualization [19, 20]. The heterogeneous lesions might be undersampled during the stereological analyses, and thus there is a need to use adaptive sampling and standardised imaging protocols [19]. As a result, there is no single synthesis of morphogenesis, structural mapping, and disease remodeling of rat lungs.

The review is a synthesis of bronchial and vascular architecture of the rat lung with focus on developmental organization, structural interdependence, and pathological remodeling. It combines morphometric, computational, and advanced imaging methods, such as μCT, optical clearing, and corrosion casting, to address discrepancies and explain the shortcomings of methods. Consolidation of the structural baseline can increase the reproducibility, increase comparisons between developmental and disease states, and better translational modeling of airway-vascular coupling. The review offers a consistent framework to answer the major conceptual and methodological gaps in the existing rat lung studies by integrating insights on normal morphogenesis and disease-related remodeling.

The review was created with the help of a narrow literature search of PubMed, Scopus, and Web of Science databases during the period between 2015 and 2025. General search combinations were used in identifying relevant studies, based on rat lung development, bronchial and vascular architecture, imaging modalities, molecular regulation, and experimental disease models. Articles that used rat lungs in imaging studies, translational experimental reports, and other structurally or mechanistically focused studies were selected, and those that lacked structural or mechanistic relevance were excluded. Citation tracking of important publications was used to add more sources. This method guaranteed the full coverage of developmental, imaging-based, molecular, and pathological factors of rat pulmonary architecture.

Developmental Morphogenesis of Rat Lung Architecture

Embryonic and Postnatal Lung Development

Rats pass through the pseudoglandular, canalicular, saccular, and alveolar phases of lung development, whereby the vascular and bronchial systems develop simultaneously to create a highly branched respiratory network. Bifurcation of airways starts at the lung buds and continues with the growing vascular plexus, which eventually develops into a hierarchical arteriovenous system [21]. Though the imaging techniques like μCT give insight into development, the fundamental process is the coordinated growth of bronchial branches and vascular structures that allow efficient respiratory architecture [22]. Models of cross-species organoid and pluripotent stem cells indicate that cardiopulmonary co-development is conserved, with epithelial and endothelial differentiation having to proceed in parallel to reach functional maturation [23]. VEGF is a key mediator of vascular bed development, and VEGF signaling defects have great consequences on alveolarization and vessel branching [24, 25]. VEGF deficiency or hypoxic stress impedes the development of the distal vessels' arborization and septation, which supports the dependence of both epithelial and vascular growth in morphogenesis [26]. Branching of the airways involves the involvement of fibroblast growth factor 10 (FGF10) and its receptor FGFR2b, and the change in these signals can change vascular alignment indirectly by regulating epithelial geometry [27]. In prenatal and postnatal stages, epithelial-mesenchymal crosstalk is proportionately controlled by signaling pathways, including SHH, WNT, and TGF-β [28, 29]. Notch-dependent signaling also enhances airway and vascular patterning through the preservation of coherent growth and the regulation of epithelial cell fate [30]. Integrative studies reveal that airway branching and vascular patterning are mutually instructive processes, with endothelial cues regulating airway topology and vice versa [31-34]. Collectively, these processes suggest that the morphogenesis of the rat lung is a highly coordinated process that is influenced by molecular gradients, juxtacrine signaling, and mechanical forces.

Cellular and Extracellular Matrix Dynamics

Morphogenesis of rat lungs involves the maintenance of constant contact between the mesenchymal and epithelial cells that form future bronchial and vascular tissues. Epithelial-mesenchymal interactions control the smooth muscle investment, angle of branching, and differentiation based on the reciprocity of a growth factor, matrix remodeling, and mechanical tension signaling loops [35, 36]. The extracellular matrix (ECM) is a structural scaffold and a signaling platform that promotes alveolarization and septation [37]. The adhesion between epithelial stability and basement membrane integrity is mediated by integrin and ensures structural maturation and controls inflammatory homeostasis [38]. The stabilization of developing vessels by paracrine signals of pericytes and fibroblasts, the dynamic response of endothelial cells to matrix stiffness and architecture, controls capillary sprouting and arteriovenous differentiation [39]. The ECM, which consists of collagens, elastin, fibronectin, and laminin, develops during both prenatal and postnatal stages to assist in alveolar recoil characteristics and growth, which is necessary for effective ventilation [40]. On the whole,

the ECM dynamics combine with the epithelial and mesenchymal signaling to develop mechanically stable but flexible airway and vascular systems.

The results of rat development should be viewed with caution since the variation in the pattern of branching and vascular alignment between strains provides variability in studies [22]. Also, integrative analyses show that epithelial-endothelial coordination is very context-dependent and thus observations made with one rat strain cannot necessarily be reliably generalized to other species or experimental conditions [31].

Coordinated airway and vascular development during different embryonic and postnatal development stages determines rat lung morphogenesis, which is regulated by reciprocal epithelial-endothelial signaling and highly controlled molecular pathways that determine patterns of branching and vascular alignment. Mechanobiological cues, the extracellular matrix, also contribute to structural support and guide maturation of the alveoli and vascular. The combination of these processes of development forms the primary bronchial-vascular architecture that forms the basis of subsequent functional performance and remodeling pathology.

Imaging and Quantitative Approaches

Classical Histomorphometry and Stereology

Histomorphometric and stereological methods have long been used in the quantitative evaluation of lung structure, which offers objective and reproducible estimates of airway and vascular parameters of fixed tissue specimens. To close the divide between architectural design and gas-exchange efficiency, first, stereological models were created to measure the alveolar volume, surface area, and capillary density [41]. Design-based stereology is still a major method used in the measurement of microvascular and bronchial architecture of rat lungs and can be reproducibly used in both developmental and pathological models. The finesse of the stereological concepts of rodents has now allowed the detailed description of the microvascular branching, the thickness of the vessel walls, and the size of the bronchial lumen in physiological and disease states [42]. Stereology, when used together with systematic uniform random sampling, removes the distortions of two-dimensional histology and provides statistically representative estimates of three-dimensional quantities [43]. In order to improve precision between tissue hierarchies, recent methods combine computed tomography with histological sections to produce multiscale datasets to be used in stereological computation [44]. Stereology remains a valid method of measuring vascular rarefaction, interstitial expansion, and bronchial remodeling in experimental rat preparations and normal lung tissue [45]. Modern multiresolution workflows can be used to take the classical stereological paradigm and transform it into a single system of analysis that allows hierarchical measurements across scales by using macroscopic volumetric data as well as microscale quantification [46]. Even though classical stereology is still destructive, it is still regarded as the gold standard of volumetric calibration of digital imaging results in rat morphometric studies [47].

Modern 3D and In vivo Imaging

Recent advances in technology have changed the two-dimensional histology of the lungs into a three-dimensional volumetric analysis of intact rat lungs, which is dynamic. The micro-computed tomography (Micro-CT or μCT) enables the determination of airway diameter, vessel density, and branching geometry at a resolution of micrometers across entire volumes of lungs [48]. Precise reconstruction of the microvasculature of the lungs can be obtained in case of proper control of perfusion pressures and contrast enhancement, and almost native visualization of the arterial and venous hierarchies can be achieved [49]. Optical clearing and light-sheet microscopy can be used as a complement to μCT, allowing mapping microvascular-bronchial relationships at a fine scale in transparent, fluorescently stained rat lungs [50]. Improvements in aerosol-based clearing techniques currently allow longitudinal

imaging of the inflammatory and infectious events *in vivo* with enhanced imaging penetration and temporal resolution [51]. Multiscale three-dimensional imaging systems combine both the macrovascular and microvascular data to produce organ-scale views of the bronchial and vascular hierarchies [52]. Computational modeling also improves such datasets through digital reconstruction of vascular networks and bronchial patterns of branching, which allows simulation of the interactions between hemodynamics and ventilatory conditions relevant to physiology [53]. These virtual lung models accurately recreate *in vivo* mechanical conditions with experimentally obtained values of pulmonary volume, pressure, and strain [54]. In fetal morphometry and developmental toxicology, it has been shown that volumetric imaging and μCT are capable of detecting small changes in airway and vascular development, which can be used to give quantitative measures of translational development [55]. High-resolution imaging, optical clearing, and computational modeling are a complete paradigm that brings together structural quantification, spatial organization, and predictive simulation.

Imaging and stereological techniques, although positive, have significant drawbacks. Stereological estimates are also prone to sampling strategy and inflation bias, which may create systematic variability among laboratories [43]. Perfusion pressure and uniformity of contrast are the key factors affecting the accuracy of μCT, which leads to inconsistent visualization of distal vessels across studies [49].

Stereology and μCT are the gold standard of volumetric and vascular reconstruction accuracy, and quantitative imaging modalities differ in the resolution of analysis at the morphometric scales (Table 1). Fig. 1 represents the workflow of the imaging and quantitative methods that were employed to analyze the morphometry of rat lungs. Fig. 2 [53] illustrates an example of high-resolution whole-lung reconstruction of a μCT of bronchial vascular architecture of intact rat lungs. The left panel is the horizontal slice of μCT that illustrates the global airway and parenchymal architecture of the rat lung, and the right one is the magnified view of the boxed area, which represents the detailed microstructure of the alveoli and acinar.

Multi-scale reconstruction of rat bronchial and vascular architecture can be done using imaging and quantitative methods - classical stereology to μCT and light-sheet microscopy. The gold-standard validation framework is provided by stereology, and the high-resolution structural mapping of organs in a comprehensive manner is offered by modern 3D imaging. Computational modeling goes a step further to combine these datasets and simulate

Table 1. Comparative Overview of Quantitative Imaging and Analytical Techniques in Rat Lung Architecture Studies

Method	Measured Parameters	Scale / Resolution	Quantitative Strengths	Best Suited Applications	Methodological Limitations
Design-based Stereology	Alveolar number, capillary length, vessel wall thickness	Micrometer	Unbiased volumetric estimates; gold standard for validation	Developmental morphogenesis, COPD, fibrosis	Destructive; sensitive to inflation and sampling; labor-intensive.
Micro-Computed Tomography (Micro-CT)	Airway volume, vascular branching, lumen diameter	1–10 μm	Whole-organ 3D visualization, high reproducibility	Vascular remodeling, developmental mapping	Dependent on perfusion/contrast; limited soft-tissue contrast.
Light-Sheet Microscopy / Optical Clearing	Microvascular alignment, airway–vessel interaction	Sub-micron	Visualizes intact networks; enables fluorescence tracking	Inflammation, regeneration, infection models	Clearing may distort tissue; poor penetration in fibrosis.
Computational Modeling / Simulation	Flow dynamics, perfusion, gas exchange	Variable (macro-to-micro)	Links structure with function; predicts physiological parameters	Hypoxia, pulmonary hypertension, toxicology	Highly input-dependent; assumptions may not reflect in vivo states.

physiological interactions, and improve interpretability. These instruments are collectively a consistent system of quantitative tools necessary to research development, remodeling, and disease in rat lungs.

Experimental Models of Lung Diseases in Rats

Models of Chronic Obstructive Pulmonary Disease (COPD) and Emphysema

The analysis of structural and vascular alterations underlying progressive airflow limitation with the help of experimental rat models of emphysema and chronic obstructive pulmonary disease (COPD) has been critical. Human COPD is characterized by the destruction of the alveoli and small airway remodeling, which are recapitulated by the classical induction methods, including cigarette smoke or proteolytic agent exposure [56]. These rats exhibit the progressive emphysematous changes, which, according to longitudinal modeling, include the quantifiable loss of parenchymal elasticity and capillary rarefaction, which follow the progression of human disease [57]. Morphometric studies demonstrate that there is an increase in the size of distal airspaces, alveolar septa become thin, and the surface area of capillaries is reduced, which increases dead space and reduces the efficiency of gas-exchange [58]. Injury in neonatal and juvenile rats caused by hyperoxia induces the same structural continuum, alveolar simplification, and vascular rarefaction occurring concurrently [59]. Combined COPD-cor pulmonale models also enable concurrent evaluation of right ventricular adaptation and pulmonary vascular remodeling, which enhances the structure-function relationships with chronic airflow limitation [60]. The characteristic architectural alterations, including thickening of the small airway walls, loss of the distal vascular density, and altered smooth-muscle organization, which are highly reminiscent of airway-vascular coupling disruptions seen in human COPD, are also identified in smoke-exposure models

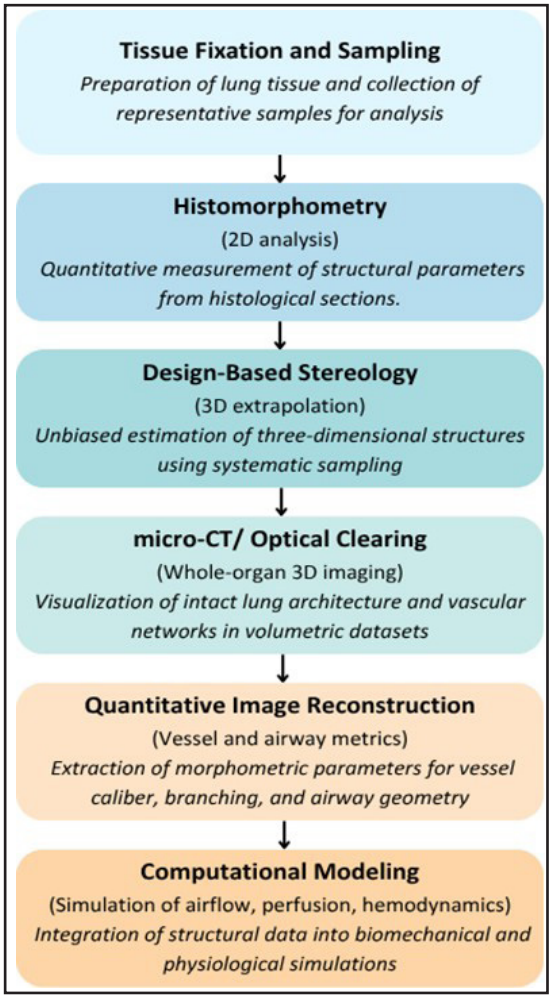


Fig. 1. Workflow of Imaging and Quantitative Approaches in Rat Lung Morphometry.

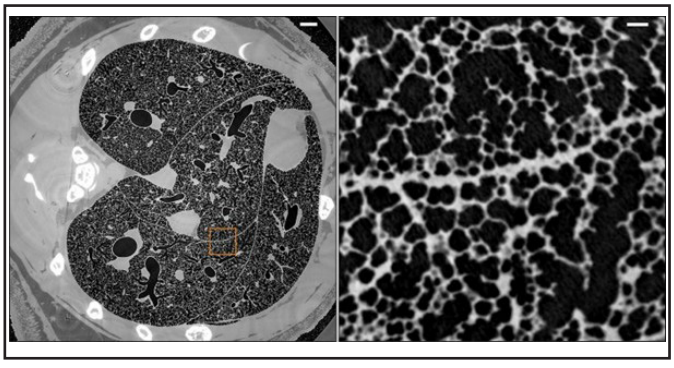


Fig. 2. Micrometer-resolution X-ray micro-CT of an intact post-mortem juvenile rat lung (reproduced from ref. [53], under CC BY 4.0 license).

[61]. Taken together, these rat models are a good representation of the morphometric and hemodynamic characteristics of COPD, which allows interventions to be controlled to protect airways and vascular integrity.

Pulmonary Hypertension and Vascular Remodeling

The rat model of pulmonary hypertension (PH) is a well-defined model for studying vascular structural remodeling. Chronic hypoxia or chemical agents like monocrotaline or Sugen cause prolonged increases in pulmonary arterial pressure, which in turn leads to the medial hypertrophy, adventitial thickening, and muscularization of the distal arteries [62]. The reversal of neointimal proliferation by therapeutic studies such as paclitaxel-based interventions demonstrates the structural reversal of neointimal proliferation, which highlights the usefulness of PH models in testing anti-remodeling strategies [63]. The Sugen-hypoxia model allows cardiac magnetic resonance imaging to be used to allow longitudinal evaluation of biventricular structural and functional responses, correlating right-heart responses with pulmonary vascular load [64]. Despite the fact that this model mainly reflects severe pulmonary arterial hypertension, related parenchymal injury, and mild patterns of emphysema indicates the structural interaction between vascular and airway compartments in the advanced disease [65]. Collectively, these PH models offer critical information about the thickening of the vascular, the stiffening of the vessel, and the hierarchical remodeling of the pulmonary arterial tree.

Asthma and Inflammatory Models

Rat models of asthma and allergic airway inflammation are the focus of structural interaction between immune activation, angiogenesis, and airway remodeling. Ovalbumin or house-dust-mite antigen sensitization results in reproducible airway hyperresponsiveness that is associated with vascular proliferation and deposition of extracellular matrix in the peribronchial region [66]. Histologically, neovascularization, goblet-cell hyperplasia, and epithelial basement-membrane thickening are always evident, and they represent the organized remodeling of vascular, mesenchymal, and epithelial compartments [67]. Interventional models of allergic inflammation indicate that structural outcomes, including decreased peribronchial vessel density or decreased smooth-muscle thickening, can be measured quantitatively in these models, which validates their usefulness in the testing of remodeling-directed therapies [68]. The models of asthma also demonstrate the presence of expanded bronchial vascular plexus and the change in vessel permeability that leads to the thickening of the airway wall and the narrowing of the lumen [69]. Taken together, these inflammatory models offer a reproducible model of evaluation of airway and vascular remodeling in an allergic state.

Fibrosis and Acute Lung Injury

Experimental models of fibrosis and acute lung injury are essential for understanding the structural distortion and reparative vascular responses that are related to chronic lung disease. Activation of macrophages, cytokine release, and matrix deposition in response to exposure to toxicants or hypoxia is highly reminiscent of human interstitial fibrosis [70]. Experiments of smoke-induced injury indicate that corticosteroid timing and dose affect vascular remodeling, collagen turnover, and final fibrotic phenotype, highlighting the structural plasticity of injured lung tissue [71]. Models based on bleomycin are still the gold standard as they offer quantitative data of anti-fibrotic activity and architectural recovery [72]. The association between oxidative stress, vascular leakage, and endothelial barrier disruption is further demonstrated using ischemia-reperfusion injury models, which can be prevented through antioxidant therapy, including edaravone [73]. Natural and synthetic interventions, such as resveratrol nano-capsules and crocin, have been demonstrated to inhibit fibrosis, inflammation, and vascular dysfunction, which contributes to their possible therapeutic significance [74, 75]. These models taken together describe the cascade of events of epithelial injury, vascular repair, and matrix remodeling that control chronic fibrotic progression.

Despite the numerous structural parallels of COPD and fibrosis, rat disease models are based on induced injuries, which may not completely recapitulate the heterogeneous, slow progression of human disease [56]. Equally, fibrosis induced by bleomycin causes homogenous parenchymal damage, unlike the focal and heterogeneous injury in the clinical presentation [72].

In structural remodeling, several of the conserved signalling cascades integrate fibrotic, inflammatory, and angiogenesis (Table 2), reflecting the molecular interdependency of the vascular and bronchial systems. Fig. 3 demonstrates the grouping of experimental rat models and the structural changes that occur in them.

Rat models of COPD, pulmonary hypertension, asthma, and fibrosis reproduce specific patterns of airway and vascular remodeling that are highly similar to human disease. Their structural effects, such as destruction of alveoli, vascular rarefaction, arterial thickening, neovascularization, and matrix deposition, allow accurate morphometric evaluation in disease conditions. Architectural variations of the models are also effective in offering a solid platform for assessing treatments that focus on airway and vascular integrity. These experimental systems as a whole constitute a complete structural toolkit to study pathological remodeling in the rat lung.

Table 2. Key Molecular Pathways and Signaling Axes Governing Pulmonary Architectural Remodeling in Rats

Disease Model	Induction Method	Bronchial Alterations	Vascular Alterations	Quantitative Metrics Commonly Used	Methodological Limitations
Chronic Obstructive Pulmonary Disease (COPD)	Cigarette smoke exposure or elastase instillation	Airway wall thickening, lumen enlargement	Vascular rarefaction, endothelial loss	Mean linear intercept, vessel density, wall thickness	Accelerated lesions; protocol and strain variability.
Pulmonary Hypertension (PH)	Sugen–hypoxia or monocrotaline administration	Minimal bronchial effect	Medial hypertrophy, intimal thickening, adventitial fibrosis	Vascular wall ratio, lumen/wall index, muscularization percentage	Produces severe lesions not fully representative of early human PH.
Asthma / Allergic Inflammation	Ovalbumin or HDM sensitization	Epithelial hyperplasia, goblet cell metaplasia	Angiogenesis, venular dilation	Basement membrane thickness, capillary number, airway smooth muscle index	Exaggerated Th2 response; high protocol dependence.
Pulmonary Fibrosis	Bleomycin or ischemia–reperfusion	Airway distortion, alveolar collapse	Capillary regression, collagen deposition	Collagen index, alveolar volume, capillary-to-fiber ratio	Uniform injury unlike patchy human fibrosis; dose-dependent variability.

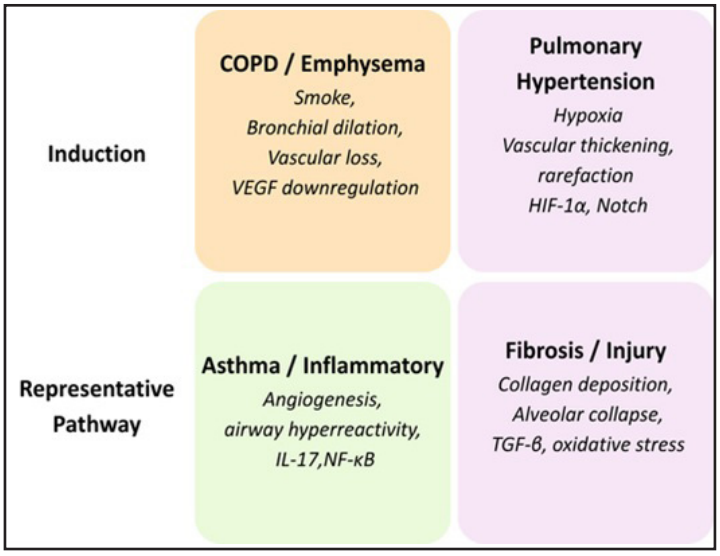


Fig. 3. Classification of Experimental Rat Models and Associated Structural Alterations.

Molecular Pathways Governing Architectural Remodeling

Key Angiogenic and Morphogenetic Pathways

In the rat lung, morphogenesis of the bronchial and vascular systems is tightly controlled by conserved molecular pathways incorporating hypoxic, angiogenic, and developmental cues. Notch signaling is a key orchestrator of endothelial specification and vascular hierarchy, in which it keeps the tip-stalk cell differentiation balanced in sprouting angiogenesis [76]. VEGF/PI3K/Akt cascade activation restores the endothelial functional activity and decreases pulmonary arterial thickening in COPD-induced vascular remodeling, which is associated

with metabolic control and angiogenic competence [77]. Hypoxia-inducible factor-1α (HIF-1α) pathway is an oxygen-sensing regulator that links hypoxic conditions to vascular growth, and its malfunctioning leads to the excessive muscularization of pulmonary hypertension [78]. Endothelial-derived angiocrine factors also influence epithelial branching and alveolar maturation, highlighting reciprocal vascular–airway communication during development and repair [79]. Interactions between PPARγ and Wnt/β-catenin signaling guide epithelial differentiation and vascular alignment, and imbalances among these networks contribute to pathological architectural remodeling [80]. VEGF, HIF-1α, Notch, and Wnt signaling constitute an integrated regulatory axis that regulates angiogenesis, epithelial-vascular interactions, and tissue homeostasis in normal and disease lung [81].

Inflammatory and Oxidative Mechanisms in Vascular Remodeling

Redox-responsive pathways and reactive oxygen species (ROS) are significant regulators of inflammatory and structural remodeling in rat models of pulmonary disease. Mitochondrial dysfunction, endothelial apoptosis, and perivascular inflammation are sustained by prolonged oxidative stress in pulmonary hypertension and remodel the vascular wall [82]. Chronic redox imbalance may trigger endothelial-to-mesenchymal transition, leading to adventitial fibrosis and microvascular obliteration, which resembles human pulmonary pathology [83]. Inflammatory cytokine activation—particularly within the NF-κB/TNF-α axis—exacerbates vascular injury and promotes smooth-muscle hypertrophy and intimal thickening in hypoxia-induced models [84]. Chronic hypoxia induces the upregulation of microRNA-150 that suppresses vascular remodeling through inhibiting profibrotic and inflammatory cascades, which rejuvenate endothelial functions and pulmonary hemodynamics [85]. All these processes indicate that there is close molecular interaction between oxidative stress, cytokine release, and regulation by microRNAs in adaptive and maladaptive remodeling of the pulmonary vasculature.

Genetic and Epigenetic Regulation of Remodeling

Genetic and epigenetic changes are increasingly recognized as key determinants in the transition from reversible injury to chronic pulmonary remodeling. Histone acetylation and methylation control transcriptional reactions to oxidative injury and vascular pathology, and environmental stressors promote dynamic histone chromatin remodeling in rat models of fibrosis and pulmonary hypertension [86]. Long non-coding RNAs and microRNAs have been shown to regulate vascular contractility and endothelial differentiation, and experimental manipulation of these RNAs has been shown to change the course of disease in rat pulmonary arterial hypertension models [87]. In chronic thromboembolic pulmonary hypertension, transcriptomic studies indicate that the patterns of gene-expression differences that regulate extracellular-matrix turnover, angiogenesis, and inflammation are heritable reprogramming of vascular and interstitial cell fate [88]. Fibroblast reprogramming studies of rodent tissues have shown that intermediate trans-endothelial-like states can increase reparative capacity, which can inform us about the mechanisms underlying structural regeneration [89]. Chromatin data of the rat parenchymal disease models on a genome-wide scale also show reproducible epigenetic signatures of vascular distortion and fibrotic development [90]. Taken together, these results indicate that genetic, epigenetic, and transcriptional regulators combine with environmental and molecular signals to determine the pathway of pulmonary architectural remodeling.

Although rat models have helped to elucidate many signaling pathways, there are still a number of translational differences. Hypoxia-regulated HIF-1α signaling differs in magnitude between species, influencing vascular-proliferative responses [78], while inflammatory pathways such as NF-κB/TNF-α activation may be exaggerated in rodent models relative to chronic human disease [84].

Angiogenic, inflammatory, and fibrotic responses are interconnected through several conserved signaling cascades in the process of structural remodeling (Table 3), which indicates the molecular interdependence of bronchial and vascular systems.

Key molecular pathways—including VEGF, HIF-1α, Notch, and Wnt/β-catenin—form a coordinated regulatory axis controlling angiogenesis and airway–vascular alignment. Maladaptive vascular remodeling is also further promoted by oxidative stress, cytokine signaling, and microRNA networks in various models of rat disease. Long-term changes in vascular and interstitial cell fate are determined by genetic and epigenetic regulators, including chromatin modulations and non-coding RNAs. A combination of these molecular systems describes the convergence of the inflammatory, angiogenic, and fibrotic responses to generate the structural remodeling.

Table 3. Structural Remodeling Patterns Across Experimental Rat Models of Lung Disease

Pathway	Key Regulators / Molecules	Primary Mechanism of Action	Associated Structural Outcome	Methodological Limitations
VEGF/PI3K/Akt	VEGF, Akt, mTOR	Promotes endothelial proliferation and repair	Restores vascular integrity; mitigates arterial thickening	Strain-dependent effects; acute models overestimate response.
HIF-1α Signaling	HIF-1α, Src, mTOR	Hypoxia-induced vascular remodeling and muscularization	Vascular hypertrophy; altered perfusion gradients	Hypoxic responses exaggerated in rats vs humans.
Notch Signaling	DLL4, Jagged1, NICD	Controls endothelial differentiation and vessel hierarchy	Balanced tip/stalk cell specification	In vivo modulation is non-specific; pathway crosstalk complicates results.
Wnt/β-Catenin–PPARγ Axis	β-catenin, PPARγ	Regulates epithelial–mesenchymal signaling and branching	Aberrant remodeling when dysregulated	Stage-dependent; rodent-specific pathway sensitivity.
Oxidative Stress / Cytokine Axis	NF-κB, TNF-α, ROS	Promotes smooth muscle proliferation and inflammation	Intimal thickening, fibrosis	Inflammatory responses often stronger in rodents.
Non-Coding RNA Networks	miR-150, lncRNAs	Epigenetic control of vascular remodeling	Fibrosis modulation, endothelial repair	Limited cross-species conservation; acute-model bias.

Integrative Translational Perspectives

Translational Relevance of Rat Pulmonary Architecture

The rat lung model has significant translational potential and offers a mechanistic understanding of clinical importance because it is closely physiologically similar to the human pulmonary system. The analysis of the single-cell gene expression and remodeling in the rat lungs is comparable to the results of human pulmonary arterial hypertension, showing that there is a shared vascular pathobiology [91]. Translational fidelity is also confirmed with aerosol-based inhalation studies, whereby the dynamics of droplet transport, deposition, and clearance scales between rat and human airway geometries can be predicted [92, 93]. Precision-cut lung slices have demonstrated that rat pulmonary tissue mimics human xenobiotic enzymatic profiles and thus can be used in preclinical drug-safety testing [94]. Also, multifaceted models of pulmonary hypertension and right-ventricular remodeling in rats recapitulate experimentally determined hemodynamic and architectural patterns, which can be used to extrapolate therapeutic targets and strategies [95]. Taken together, this establishes that the rat offers a physiologically healthy platform that connects preclinical mechanistic data to human lung pathophysiology.

Integrating Morphometric and Molecular Frameworks for Precision Modeling

The rat lung has turned out to be a useful platform to combine molecular and structural data, which are fueled by multimodal imaging and omics technologies. Quantitative morphometric analysis, which is coupled with high-resolution imaging, provides reproducible spatial measures of airways, vessels, and parenchyma that are translational biomarkers of emphysema and pulmonary fibrosis [96, 97]. Three-dimensional reconstruction and optical imaging methods directly observe multiscale structural remodeling and also record molecular correlates of inflammation and tissue repair [98]. Regional density and vascular tortuosity are imaging biomarkers that have a strong association with histopathological severity in rat models and parallel imaging phenotypes in human interstitial lung disease [99]. Computational registration and cross-species anatomical mapping improve comparative knowledge of bronchiolar and lobular structure in rodents and humans [100]. Transcriptomic analysis of rat and human airway epithelium also shows that there is a conserved gene-network regulation of epithelial differentiation and immune responses [101, 102]. A combination of these integrative approaches combines molecular profiling

with quantitative morphometry to produce reproducible, cross-compatible data sets that enhance translational pulmonary modeling.

Computational Extrapolation and Cross-Species Validation

Computational models are increasingly allowing one to extrapolate rat data to human respiratory states. Now species-agnostic comparisons of lung cell populations can be made using single-cell atlases and transcriptomic mapping, which can be used to predict species-conserved vascular-signaling and matrix-remodeling pathways [103, 104]. Simulations in silico are reliable predictors of particle transport, dose distribution, and deposition efficiency when flow dynamics and airway geometries of rats are scaled to human conditions [105]. Combining computational results with morphometric and molecular data can be used to create digital lung twins that can recreate physiologic behavior across species. The use of these models in comparison to empirical data of rat and human systems improves algorithms to predict gas exchange, mechanical stress, and drug-absorption profiles. This integration of computational surrogate and biological validation makes the rat model a predictive translational system rather than a descriptive experimental system, and makes it more relevant to accurate respiratory research.

Although there are strong parallels in the translation, species-specific differences do not allow direct extrapolation of rat-based results. Single-cell studies indicate partial but not complete correspondence of rat and human vascular signaling networks [91], and xenobiotic metabolism, while broadly similar, still differs in key enzyme pathways relevant for drug-response prediction [94].

Rat lungs exhibit physiological, metabolic, and structural characteristics that are highly similar to those of the human lungs, which makes them highly translational. A combination of morphometric data and molecular and imaging-based analyses would allow cross-species biomarkers of structural lung disease to be reproducible. Predictions of gas exchange, airflow dynamics, and drug delivery are also enhanced with the help of computational scaling and digital models of lung twins. Collectively, these strategies make the rat a strong translational tool between the experimental results and the human pulmonary pathophysiology.

Emerging Technologies in Pulmonary Structural Analysis

Advanced Imaging and Quantitative Modeling

Recent breakthroughs in quantitative modeling and computational imaging have revolutionized the study of pulmonary structure and vascular remodeling using rat models, where μCT imaging can be used to visualize microvascular adaptation to hemodynamic or hypoxic stress with high spatial resolution, and the patterns of remodeling heterogeneity can be used to better understand cardiopulmonary coupling in pulmonary hypertension [107]. Computational models that take morphometric inputs reproduce airflow distribution, pressure gradient, and vascular resistance through fluid dynamics and tissue deformation simulation of the rat lung [108]. Such combined approaches combine both anatomical measurements and functional performance to improve the accuracy of preclinical disease modeling and therapeutic assessment.

Bioengineered Lung Models and Translational Interfaces

Microengineered bio-platforms have become capable of recreating key rat lung biomechanical and microvascular physiological features. Lung-on-chip and 3D-printed scaffolds are alveolar-capillary interfaces re-engineered with microfluidic channels covered with epithelial and endothelial cells, and allow dynamic modeling of inflammatory, fibrotic, or mechanical stimuli [109]. These devices can manipulate airflow, perfusion, tissue stretch, and gas-exchange parameters in a controlled manner, usually based on imaging-based templates of rat lung architecture. These bioengineered systems can be used to support physiologically relevant testbeds, which can be used to further preclinical validation of

molecular and pharmacologic intervention and translational alignment between human pathology and rat *in vivo* experiments.

Integrative Systems Biology and Predictive Analytics

The imaging, molecular, and computational datasets are becoming more and more integrated into systems biology approaches to produce predictive frameworks of pulmonary remodeling. Data integration using artificial intelligence links structural, transcriptional, and metabolic networks together, providing a mechanistic understanding of inflammation, fibrosis, and angiogenesis [110]. These models integrate multi-omics data with morphometric data to project architectural changes in both development and disease. The integration of digital morphometry and systems-level models provides a platform of accurate and multiscale predictions of lung behavior and facilitates the design of interventions.

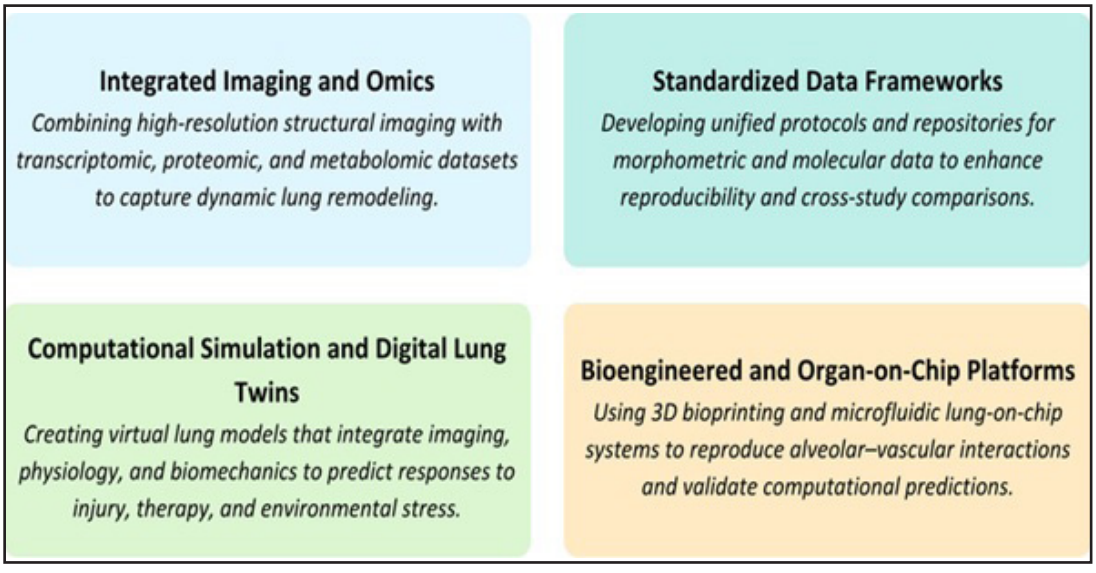
Future Directions in Technological Integration

Further convergence of systems biology, computational modeling, and state-of-the-art imaging will be useful in future pulmonary structural studies. Dynamic analysis of the co-evolution of airway branching and vascular remodeling throughout disease progression will be possible using high-resolution visualization with biomechanical and molecular data. Creating open-access, standardized morphometric and multi-omics data repositories will enhance reproducibility and translational applicability between rat models and human experiments. The combination of digital simulations and bioengineered organ-level systems into predictive multiscale models is the next step in the analysis of pulmonary structure, which correlates structure, function, and molecular regulation at never-before-seen levels. The directions in this field are new and summarized in Fig. 4.

New technologies are still limited to methodological inconsistency, with μCT segmentation and quantification being reliant on the calibration of scanners and perfusion status [107], and computational simulations being susceptible to minor morphometric errors, which can cause a considerable change in the distribution of predicted airflow or pressure [108].

The high-precision analysis of rat lung structure is now possible due to the use of advanced μCT imaging, computational modeling, and multiscale reconstruction. Physiologic microenvironments, such as lung-on-chip systems, are bioengineered platforms that are used to improve preclinical modeling and translational testing. The integration of morphometric and molecular data by systems biology and AI also produces predictive and

Fig. 4. Future Directions in Pulmonary Structural Research.



cross-scale models of lung remodeling. Further advancements will be based on integrating digital simulations, high-resolution images, and open-access data to enhance translational relevance.

Conclusion

The rat lung is an immensely informative model for studying the coordinated architecture of bronchial and vascular systems throughout development and pathology. The development of imaging, stereology, and molecular profiling has enhanced the knowledge of the interaction and remodeling of these compartments in diseases like fibrosis, pulmonary hypertension, and airway injury. The combination of morphometric accuracy with molecular and computational data is now used to improve the predictive and translational usefulness of rat studies. Further advancements in the standardization of imaging, multiscale data analysis, and analytical processes will enhance the usefulness of this model as an essential linkage between experimental discovery and human pulmonary biology.

Acknowledgements

The authors gratefully acknowledge the support of the Department of Cytology, Embryology, and Histology; Department of Pharmacognosy as well as the Department of Human Anatomy and Medical Terminology at Azerbaijan Medical University, Baku, for providing institutional assistance and access to academic resources. The authors also extend their appreciation to colleagues whose insights and constructive discussions contributed to the refinement of this review.

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Funding Sources

This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Statement of Ethics

This article is based on previously published studies and does not involve any new experiments with human participants or animals performed by any of the authors.

Disclosure Statement

The authors declare no conflicts of interest regarding the publication of this review article.

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