Comparative anatomy of respiratory bronchioles and lobular structures in mammals

Yumi Umeda [1,†,#], Takeshi Izawa[2,†], Kei Kazama[3], Sachiko Arai[3], Junichi Kamiie[4], Shinichiro Nakamura[5], Kazuki Hano[6], Masaki Takasu[6,7], Akihiro Hirata[7,8], Susanne Rittinghausen[9], Shotaro Yamano[1,#]

[1] National Institute of Occupational Safety and Health, Japan, Organization of Occupational Health and Safety, 2-26-1 Muraoka-higashi, Fujisawa, Kanagawa 251-0015, Japan

[2] Laboratory of Veterinary Pathology, Osaka Metropolitan University Graduate School of Veterinary Science, 1-58 Rinku-Orai-Kita, Izumisano, Osaka 598-8531, Japan

[3] Department of Veterinary Medicine, Azabu University, School of Veterinary Medicine, 17-71 Fuchinobe 1-chome, Chuo-ku, Sagamihara 252-5201, Japan

[4] Laboratory of Veterinary Pathology, School of Veterinary Medicine, Azabu University, 1-17-71 Fuchinobe, Chuo-ku, Sagamihara, Kanagawa 252-5201, Japan

[5] Laboratory of Laboratory Animal Science, School of Veterinary Medicine, Azabu University, 1-17-71 Fuchinobe, Chuo-ku, Sagamihara, Kanagawa 252-5201, Japan

[6] Gifu University Institute for Advanced Study, Gifu University, 1-1 Yanagido, Gifu, 501-1193, Gifu, 501-1193, Japan

[7] Center for One Medicine Innovative Translational Research (COMIT), Gifu University, 1-1 Yanagido, Gifu, 501-1193, Gifu, 501-1193, Japan

[8] Laboratory of Veterinary Pathology, Joint Department of Veterinary Medicine, Faculty of Applied Biological Sciences, Gifu University, 1-1 Yanagido, Gifu, 501-1193, Japan

[9] Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM), Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany.

short running head: Comparative anatomy of Lungs

†Yumi Umeda and Takeshi Izawa have contributed equally to this work

#correspondence

Corresponding Authors:

Yumi Umeda

National Institute of Occupational Safety and Health, Japan Organization of Occupational Health and Safety, 2-26-1 Muraoka-higashi, Fujisawa, Kanagawa 251-0015, Japan

Email: umeda-yumi@h.jniosh.johas.go.jp

TEL: +81-466-54-9711

FAX: +81-466-54-9723

Shotaro Yamano

National Institute of Occupational Safety and Health, Japan Organization of Occupational Health and Safety, 2-26-1 Muraoka-higashi, Fujisawa, Kanagawa 251-0015, Japan

Email: shotaro-yamano@pulmpath.com

TEL: +81-466-54-9711

FAX: +81-466-54-972

Abstract

Rodents are widely used to study the toxicity of chemicals, but differences between species mean that results from rodents are not always directly transferrable to humans. The health of workers exposed to various chemicals and particulates in high doses or for long durations is at risk. The respiratory bronchioles and lobular structures are key sites for occupational lung diseases like pneumoconiosis, but these structures vary among animal species. Understanding these differences is crucial for studying the pathology of human occupational lung diseases. However, there is a lack of reviews focusing on these structures across different species. This review explores the lung anatomy of various mammals and its functional importance in disease to connect animal studies with human occupational lung diseases. Our results indicate that artiodactyls, especially small pig breeds and goats, are ideal for research because their respiratory bronchioles and lobular structures are similar to those of humans. This review aims to enhance the use of experimental animal data and improve our understanding of human occupational lung diseases, facilitating early detection, treatment, and prevention.

Key words: Comparative anatomy, Respiratory bronchiole, Lobular structure, Interlobular septum, Lung

Introduction

Rodents, such as rats and mice, are the most commonly used animals for studying chemical toxicity. However, species differences must be considered when applying findings from rodents to humans. A number of studies have compared animal and human lungs in terms of gas exchange and ventilation[1,2], tissue responses to particulate toxicity[3], particulate deposition and clearance[4], and lung high-resolution computed tomography (HRCT) images[5]. Research using genetically modified mice for lung stem cell studies[6–9] has highlighted anatomical differences between the mouse and human lung[6]. Animals with different lung anatomy may not adequately model human lung diseases. Accurate understanding of lung structure and cellular composition is essential in order to establish suitable experimental animal models for evaluating chemical/particulate toxicity and understanding lung disease pathology.

Workplaces are key settings where exposure to chemicals/particulates can occur. Workers exposed to high concentrations or for prolonged periods of time to a variety of chemicals are at risk of developing lung diseases, including pneumoconiosis, an occupational lung disease caused by inhaling dust and fibers. Early symptoms may be absent, and not everyone exposed will develop lung lesions, leading to lack of recognition of developing disease, and resulting in diagnosis only at advanced stages of the dissease[10]. Therefore, appropriate experimental animals are needed for accurate understanding, early detection, treatment, and prevention of pneumoconiosis and other lung diseases resulting from inhalation of toxic chemicals/particulates. Respiratory bronchioles are notably affected by particle deposition, particularly in coal miners[11,12]. Asbestosis, silicosis, and mixed-dust fibrosis, the most common pneumoconioses, show significant fibrosis of respiratory bronchioles and alveolar ducts[12–16]. The lung's

lymphatic system removes inflammatory cells and damaged tissue caused by particulate matter and microorganisms[17], with subpleural and interlobular lymphatics being the main routes[18]. CT imaging of pneumoconiosis often shows small nodules in centrilobular regions and thickened interlobular septa[19], indicating incomplete removal of the deposited material and the importance of lung anatomy.

Changes in the lungs of Japanese workers exposed to cross-linked water-soluble acrylic acid polymers (CWAAP) suggest pneumoconiosis. While inorganic dust is known to cause pneumoconiosis, there is no established evidence for organic dust. Thus, research on CWAAP-induced disease onset is needed. Workers inhaling CWAAP showed fibrosis in the respiratory bronchioles and pleural and interlobular septal fibrosis[20]. In rats, changes were limited to the alveolar regions, with interstitial fibrosis of alveolar septa[21,22]. Although fibrosis was noted, the development of fibrosis and the causative factors may have differed in rats and humans, as fibrosis developed in different areas of the lung in rats and humans. Therefore, animals with respiratory bronchioles and interlobular septa similar to those in humans are required to study this pathology.

In this review, the definitions of respiratory bronchioles and lobular structures are based on the following references[23–25]. Briefly, respiratory bronchioles are defined as the transition zone between the conducting airways and the respiratory air spaces[23]. They have structures similar to non-respiratory bronchioles except for the presence of openings for alveoli in their walls and shorter epithelial cells. Secondary lobules, as proposed by Miller[24] and Reid[25], are defined as the smallest units of lung structure, bordered by connective tissue septa (interlobular septa).

Comparative anatomical studies on respiratory bronchioles and pulmonary lobule structures are crucial for understanding human occupational respiratory diseases. They will also benefit researchers studying human respiratory diseases. However, comprehensive reviews focusing on these structures across different animal species are limited[23]. The aim of this review is to provide an overview of the morphology and function of human respiratory bronchioles and pulmonary lobule structures and detail these structures in different animals to identify the best animal models for studying occupational respiratory diseases.

Material used for the overview of the lung histology

All animal species presented in this review are listed in Table 1 and Table 2. Gross images and histopathological images using HE-stained slides were observed by us for the animal species listed in Table 1.

Lung tissues of rats and mice were provided by the Japan Bioassay Research Center, Microminipig lung tissues were provided by Gifu University, domestic pig, goat, and cow lung tissues were provided by Azabu University, and Naked Mole-Rat were provided by Kumamoto University. Whole slide images of gray squirrel, chinchilla, capybara, squirrel monkey, goat, reindeer, alpaca, donkey, pantropical spotted dolphin, black rhinoceros, bengal tiger, Japanese raccoon dog, Chinese wolf, and koala were provided by Osaka Metropolitan University.

Information on the presence or absence of respiratory bronchioles and interlobular septa was obtained from published articles (Table 2)[23,26–31]. The number of lung lobes for each of the animals in Tables 1 and 2 was also obtained from published articles[23,32–38].

Morphology and Function of Human Bronchioles and Lung Lobular Structure

The human trachea forms a complex system of branching airways known as the "bronchial tree," which undergo approximately 23 divisions[39]. As these airways branch, their number increases while their diameter decreases. In the peripheral airways, including the respiratory bronchioles, the cross-sectional area and total volume increase dramatically, slowing down the air flow until it nearly stops in the periphery[40]. Most of the airways are lined with pseudostratified ciliated epithelial cells, which decrease in height towards the periphery. The airway mucosa includes goblet cells, serous cells, and acinar cells in the submucosal glands[41]. The coordinated activity of cilia and goblet cell secretions forms the mucociliary escalator, essential for removing inhaled particles from the lungs. The alveolar epithelium mainly consists of type I alveolar epithelial cells for gas exchange and type II alveolar epithelial cells for surfactant production. Alveolar macrophages process and remove inhaled particles, initiate immune responses, and protect the alveoli[42].

Respiratory bronchioles, located between the terminal bronchioles and alveolar ducts, give rise to alveoli. This region is prone to specific lesions due to: 1) areas of poor ventilation where fine particles accumulate, potentially affecting nearby respiratory bronchioles; 2) being a transitional zone where air moves between narrow and wide spaces, causing complex airflow and stasis; and 3) the lack of cilia in respiratory bronchiolar epithelial cells, making clearance less effective. These factors make the respiratory bronchioles sites of potential vulnerability in the lung, for example, respiratory bronchioles are a common site for diffuse lung diseases like

pneumoconiosis. Therefore, studying occupational respiratory diseases using animals without respiratory bronchioles may underestimate the impact of inhaled chemicals and particulates.

The interlobular septa, seen as connective tissue sheaths extending from the pleura into the lung parenchyma, contain lymphatic vessels and veins[12]. Pulmonary lymphatic vessels protect the lungs from airborne particles and microorganisms, allow fluid influx, and remove foreign substances and damaged tissue, keeping the lungs clean. Impairment of this function can lead to lesions. Thickening of the interlobular septa is a common feature in CT images of pneumoconiosis patients[19]. The presence of lobular structures significantly influences lung lesion morphology. Thus, studying occupational respiratory diseases in animals with lobular structures is crucial for understanding the histopathology of human lung diseases.

This review examines the presence or absence of respiratory bronchioles and lobular structures in the lungs of various experimental and domestic animals. Based on findings from our research (Table 1) and the accumulated knowledge in the literature (Table 2), we discuss the optimal animal species for studying occupational respiratory diseases in humans.

Rodents

Rats (*Rattus norvegicus*) and mice (*Mus musculus*) are commonly used laboratory animals. Their lungs do not contain either respiratory bronchioles or lobular structures. While human lungs exhibit a polygonal pattern on the surface due to lobular structures, this pattern is absent in rats (Fig. 1A, B) and mice (Fig. 2A, B). Microscopic

examination also fails to reveal connective tissue separating lobules in these rodents (Fig. 1C, Fig. 2C). Thus, the lobular structure seen in humans is absent in rats and mice. Figures 1 and 2 show the lack of respiratory bronchioles in rats (Fig. 1D, E) and mice (Fig. 2D, E). Furthermore, their visceral pleura and interstitial connective tissue are relatively thin compared to domestic animals and nonhuman primates[43]. Notably, our inhalation studies with rats and mice using nanomaterials like indium tin oxide (ITO) particles[44], multi-walled carbon nanotubes (MWCNT)[45–47], and titanium dioxide nanoparticles[48,49] revealed no interlobular septa lesions or identifiable lobular structure lesions.

To find rodents with lung structures more similar to humans, we studied some unique rodent species. In the naked mole-rat (*Heterocephalus glaber*), the longest-living rodent with a lifespan of about 30 years, the lung surface did not exhibit the polygonal pattern during gross examination (Fig. 3A, B). Histological examination also showed no interlobular septa or respiratory bronchioles (Fig. 3C, D, E). Similarly, the gray squirrel (*Sciurus carolinensis*) and the chinchilla (*Chinchilla lanigera*)（Table 1）, gerbil (*Meriones unguiculatus*), hamster (*Mesocricetus auratus*), guinea pig (*Cavia porcellus*), and rabbit (*Oryctolagus cuniculus*) [23](Table 2) also lacked both interlobular septa and respiratory bronchioles. The capybara (*Hydrochoerus hydrochaeris*), the largest rodent with a body weight of 47 kg, also did not show the polygonal pattern or interlobular septa on the lung surface (Fig. 4A, B). However, respiratory bronchioles were observed in the capybara, making it the only rodent in this study with such a feature (Table 1, Fig. 4C). These findings suggest that larger body size may contribute to the presence of respiratory bronchioles in rodents, but it does not lead to the development of lobular structures.

Nonhuman Primates

In cynomolgus monkeys (*Macaca fascicularis*), a common primate used in research, the polygonal pattern present in human lungs could not be observed on the lung surface (Fig. 5A). Consistent with this, no lobular structures were found in the lungs (Fig. 5B). However, respiratory bronchioles were clearly visible (Fig. 5C, D). The presence of airway smooth muscle tissue beneath the bronchiolar epithelium made the alveolar structures in the respiratory bronchioles easily identifiable. The lung surfaces of the common marmoset（*Callithrix jacchus*）also showed neither a polygonal pattern (Fig. 5E) nor microscopic interlobular septa (Fig. 5F). In contrast, respiratory bronchioles were easily observed (Fig. 5G). Similarly, in squirrel monkeys (*Saimiri sciureus*), we observed respiratory bronchioles but not the lobular structures (Table 1). Rhesus monkeys (*Macaca mulatta*) [50], the most used nonhuman primate experimental animal in certain types of experiments such as vaccine trials, have also been reported to have respiratory bronchioles, but few interlobular septa [23,26](Table 2). No clear anatomical differences could be identified between the Old World monkeys, cynomolgus monkeys and rhesus monkeys, and the New World monkeys, common marmosets and squirrel monkeys, and respiratory bronchioles were observed in both, but no clear lobar structures were found.

Non-human primates used in nonclinical safety studies have lungs more anatomically similar to human lungs than those of rats and mice. This similarity is due to the presence of cartilage and submucosal glands in their bronchial tubes and the existence of respiratory bronchioles[32]. However, we found no evidence of the presence

of lobular structures, which are critical sites for occupational lung diseases. Therefore, our investigation indicated that no primate species had both respiratory bronchioles and lobular structures comparable to those in humans.

Cetartiodactyla

In pigs (*Sus scrofa domesticus*), both respiratory bronchioles and interlobular septa are present (Table 1). Figure 6A shows the appearance and lobular structure of the pig lung, which has four lobes on the right and three on the left. The Microminipig[51], bred for research, displays a clear polygonal pattern on the lung surface (Fig. 6B, C) and well-defined interlobular septa (Fig. 6D). Histologically, the microminipig lung is divided by thin connective tissue and vasculature (Fig. 7A-D). Distal to the terminal bronchioles, respiratory bronchioles are seen, where bronchiolar epithelium and alveolar epithelium coexist, supported by smooth muscle (Fig. 7E). Therefore, pigs, unlike rats and mice, have a lung structure similar to that of humans due to their prominent interlobular septa. The Mizo local pig, reared in Mizoram highlands, has thick visceral pleura and interlobular septa with elastic fibers, potentially enhancing lung elasticity and well-developed respiratory bronchioles improving respiratory efficiency[52]. This makes pigs sensitive models for studying diseases involving the interlobular septa. Minipigs are also used for studying infectious diseases[53,54] and COPD, a leading cause of human mortality[55,56]. Additionally, cystic fibrosis (CF), caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, affects both humans and pigs[57,58]. In particular, CF studies of the lung using pigs are known to have advantages over studies using mice, due to their well-developed sub-mucosal glands[59,60]. Thus, pigs

have a lung structure suitable for evaluating human respiratory disease pathology and will be valuable for respiratory disease research, potentially accelerating early detection, treatment, and prevention of human respiratory diseases.

Goat (*Capra Linnaeus*) lungs also exhibit both respiratory bronchioles and interlobular septa (Table 1). In goat lungs, a partial polygonal pattern can be observed (Fig. 8A), and cross-sectional and histopathological examination reveals distinct interlobular septa in continuity with the pleura (Fig. 8C). However, while interlobular septa are present, the pattern of interlobular septa does not appear to be as well developed as in the pig (Fig. 8B). On the other hand, respiratory bronchioles are more distinct in the goat compared to pigs (Fig. 8E).

In the lungs of cows (*Bos taurus*), both respiratory bronchioles and interlobular septa are prominent (Table 1). A polygonal pattern can be seen macroscopically (Fig. 9A, B), and connective tissue and vasculature define interlobular septa histologically (Fig. 9C, D). Respiratory bronchioles with mixed bronchiolar epithelium and alveoli are also observed (Fig. 9E). The lungs of the alpacas (*Vicugna pacos*) (Table 1) and camels (*Camelus Linnaeus*)[27,61], two members of the family Camelidade, also have both interlobular septa and respiratory bronchioles. Silicosis can develop in camels and, similarly to humans, is associated with diffuse to nodular fibrosis due to dust accumulation, with thickened interlobular septa and interalveolar septa infiltrated by fibrous tissue and inflammatory cells[27]. The lungs of reindeers (*Rangifer tarandus*) (Table 1) and sheep (*Ovis aries*)[23] (Table 2), which belong to the family Cervidae, also possess respiratory bronchioles and interlobular septa. These Cetartiodactyla species, having both respiratory bronchioles and lobular structures, may also be suitable for studying human occupational respiratory diseases.

In contrast, the pantropical spotted dolphin (*Stenella attenuata*), a marine Cetartiodactyla species, has different bronchial and alveolar structures. The bronchial and lung structure of the dolphin is schematized in Figure 10A. The lobular structure was unclear in the dolphin lungs (Fig. 10B), while their terminal bronchioles and alveoli were distinct, with cartilage extending to the distal bronchioles (Fig. 10C). Numerous well-developed myoelastic sphincters (MES) formed circular expansions around the terminal bronchiole (Fig. 10C), creating constrictions (Fig. 10C, D). Unlike terrestrial species, dolphin alveoli have shallow depressions. This unique structure suggests MES regulate airflow, protecting alveoli and maintaining gas exchange in marine species in the deep sea[62].

Other species

In the order Perissodactyla, both donkeys (*Equus asinus*) and black rhinoceroses (*Diceros bicornis*) showed a slight polygonal pattern on the lung surfaces (Table 1). Donkeys and black rhinoceroses had interlobular septa but not as pronounced as pigs, and respiratory bronchioles were not identified. Horses also have interlobular septa, but with incomplete septal separation of lobules[29]. Thus, horses differ from pigs, which have pronounced interlobular septa. In addition, the lungs of horses (*Equus caballus*) have been reported to be devoid of respiratory bronchioles（Table 2）[23,29]. This suggests that although hoofed ungulates, including various terrestrial even-toed ungulates, have lobulated lung structures, only a limited number of animal species have both interlobular septa and respiratory bronchioles.

In the order Carnivora, Bengal tigers (*Panthera tigris tigris*), Japanese raccoon dogs (*Nyctereutes viverrinus viverrinus*), and Chinese wolves (*Canis lipus chanco*) lack interlobular septa but have prominent respiratory bronchioles (Table 1). Dogs (*Canis familiaris*), including beagle dogs, which are often used in experiments, also have notable respiratory bronchioles with branching patterns similar to those in humans[23,30] (Table 2). Ferrets (*Mustela putorius furo*), known to possess respiratory bronchioles, are considered better human models than rodents[31](Table 2). Kock *et al*. found that inhalation exposure of rats, monkeys, and ferrets to ozone caused more severe acute damage to the lung epithelium in ferrets, which like humans and monkeys have respiratory bronchioles, than in rats[31]. As discussed above, some Carniviora have well-developed respiratory bronchioles and are useful models for the human peripheral airways, but they are not appropriate as models for assessing the effects of the septum as similarly to rats and mice they lack interlobular septa. In the order Marsupialia, koalas (*Phascolarctos cinereus*) have neither lobular structures nor respiratory bronchioles (Table 1).

Discussion and conclusion

Using pigs, particularly miniature pigs like minipig and Microminipig, can bridge the gap between the results from rodent studies and human clinical studies, enhancing our understanding of respiratory diseases in humans. Minipigs are commonly used in regulatory toxicity studies, with the Göttingen minipig being the preferred choice in Europe, and their use is accepted by regulatory authorities[63]. In Europe, minipigs are increasingly replacing beagle dogs in safety pharmacology studies[63]. Already, Koch *et*

al. at the Fraunhofer Institute in Germany have developed an inhalation model for Göttingen minipigs[64]. This model includes a mask that ensures precise and reproducible delivery of aerosol and gaseous substances to the airways. They have also developed a head-only exposure system and demonstrated the particle size dependence of lung deposition using a chemical tracer method[65].

Pigs have respiratory bronchioles and lobular structures, making them ideal for studying occupational respiratory diseases like pneumoconiosis. In addition to the ethical issues that need to be considered when experimenting with nonhuman primates, miniature pigs are more suitable for inhalation studies of environmental hazards compared to nonhuman primates and beagle dogs. We are currently developing a technique to administer a chemical suspension directly into the lungs of pigs, similar to the intratracheal administration method used in rodents.

The review re-confirms that even-toed ungulates have prominent respiratory bronchioles and lobular structures. Pigs have more pronounced lobular structures than humans, making them sensitive to changes such as interlobular septa thickening. Goats have even more developed respiratory bronchioles than pigs, potentially making them more sensitive to lesions like silicotic nodules and asbestos lung. The manageable size of miniature pigs and miniature goats makes them suitable for long-term experiments to induce chronic diseases like end-stage pulmonary fibrosis, lasting up to two years. We are planning a study in which Microminipigs will be administered asbestos and observed for two years to test the ability of this animal model to detect carcinogenicity.

Recent advancements, such as single-cell RNA sequencing (scRNA-seq), have identified novel cell subsets in the respiratory organs of both healthy and diseased humans, which provides new insights into disease pathology[66–70]. Studies have shown

that AT0/RAS cells, specifically found in the respiratory bronchioles, are present in ferrets[71] and monkeys[72], but not in mice, highlighting significant species differences at the single-cell resolution level. We have confirmed that these cell subsets are abundant in Microminipig lungs (data not shown).

Utilizing new research methods and selecting suitable experimental animals will advance our understanding of human respiratory diseases, leading to early detection, improved treatment, and preventive strategies.

Disclosure of Potential Conflicts of Interest

The authors have no competing interests to disclose.

Acknowledgments

We thank Misae Saito (National Institute for Occupational Safety and Health) for assistance with the preparation of the pathological specimens, Kinji Kobayashi (Shin Nippon Biomedical Laboratories, Ltd.) for providing the histopathological specimen of the cynomolgus monkey, and Aya Umeda for drawing the silhouette diagrams of the animals in the figures and the lung structure of the Microminipigs and dolphins. We received samples from the "Kumadai-Deba" naked mole-rat research sample supply system at Kumamoto University, with the support of Prof. Kyoko Miura. We also wish to thank Dr. David B. Alexander of Nanotoxicology project, Nagoya City University Graduate School of Medicine for his insightful comments and English editing.

This work was supported by JSPS KAKENHI (no. 23H03157 to SY), and a grant-in-aid from the Japan Organization of Occupational Health and Safety (Collaborative Research to YU).

References

1. West JB. How Well Designed Is the Human Lung? Am J Respir Crit Care Med 173: 583–584. 2006.
2. West JB, Watson RR, and Fu Z. The human lung: did evolution get it wrong? European Respiratory Journal 29: 11–17. 2007.
3. Francis H. Y. G, Vallyathan V, and Hahn FF. Comparative pathology of environmental lung disease: an overview. Toxicol Pathol 35: 136–147. 2007.
4. Snipes MB, McClellan RO, Mauderly JL, and Wolff RK. Retention Patterns for Inhaled Particles in the Lung: Comparisons Between Laboratory Animals and Humans for Chronic Exposures. Health Physics 57: 69. 1989.
5. Chen Q, Klein JS, Gamsu G, and Webb WR. High-resolution computed tomography of the mammalian lung. Am J Vet Res 53: 1218–1224. 1992.
6. Tata PR, and Rajagopal J. Plasticity in the lung: making and breaking cell identity. Development 144: 755–766. 2017.
7. Wansleeben C, Barkauskas CE, Rock JR, and Hogan BLM. Stem cells of the adult lung: their development and role in homeostasis, regeneration, and disease. WIREs Developmental Biology 2: 131–148. 2013.
8. Baron RM, Choi AJS, Owen CA, and Choi AMK. Genetically manipulated mouse models of lung disease: potential and pitfalls. American Journal of Physiology-Lung Cellular and Molecular Physiology 302: L485–L497. 2012.
9. Rock JR, Randell SH, and Hogan BLM. Airway basal stem cells: a perspective on their roles in epithelial homeostasis and remodeling. Dis Model Mech 3: 545–556. 2010.
10. DeLight N, and Sachs H. Pneumoconiosis. StatPearls Publishing. Treasure Island (FL). 2024.
11. Pinkerton KE, Green FH, Saiki C, Vallyathan V, Plopper CG, Gopal V, Hung D, Bahne EB, Lin SS, Ménache MG, and Schenker MB. Distribution of particulate matter and tissue remodeling in the human lung. Environmental Health Perspectives 108: 1063–1069. 2000.
12. Mukhopadhyay S. Non-Neoplastic Pulmonary Pathology: An Algorithmic Approach to Histologic Findings in the Lung. Cambridge University Press. Cambridge. 2016.
13. Roggli VL, Gibbs AR, Attanoos R, Churg A, Popper H, Cagle P, Corrin B, Franks TJ, Galateau-Salle F, Galvin J, Hasleton PS, Henderson DW, and Honma K. Pathology of asbestosis- An update of the diagnostic criteria: Report of the

asbestosis committee of the college of american pathologists and pulmonary pathology society. Arch Pathol Lab Med 134: 462–480. 2010.
14. Wright JL, and Churg A. Morphology of small-airway lesions in patients with asbestos exposure. Human Pathology 15: 68–74. 1984.
15. Anna-Luise A. Katzenstein. Diagnostic Atlas of Non-Neoplastic Lung Disease: A Practical Guide for Surgical Pathologists. Demos Medical. 2016.
16. Honma K, Abraham JL, Chiyotani K, De Vuyst P, Dumortier P, Gibbs AR, Green FHY, Hosoda Y, Iwai K, Williams WJ, Kohyama N, Ostiguy G, Roggli VL, Shida H, Taguchi O, and Vallyathan V. Proposed criteria for mixed-dust pneumoconiosis: definition, descriptions, and guidelines for pathologic diagnosis and clinical correlation. Hum Pathol 35: 1515–1523. 2004.
17. Schraufnagel DE. Lung lymphatic anatomy and correlates. Pathophysiology 17: 337–343. 2010.
18. Sozio F, Rossi A, Weber E, Abraham DJ, Nicholson AG, Wells AU, Renzoni EA, and Sestini P. Morphometric analysis of intralobular, interlobular and pleural lymphatics in normal human lung. J Anat 220: 396–404. 2012.
19. Akira M. Uncommon pneumoconioses: CT and pathologic findings. Radiology 197: 403–409. 1995.
20. Kishimoto T, Okamoto K, Koda S, Ono M, Umeda Y, Yamano S, Takeda T, Rai K, Kato K, Nishimura Y, Kobashi Y, and Kawamura T. Respiratory disease in workers handling cross-linked water-soluble acrylic acid polymer. PLOS ONE 18: e0284837. 2023.
21. Takeda T, Yamano S, Goto Y, Hirai S, Furukawa Y, Kikuchi Y, Misumi K, Suzuki M, Takanobu K, Senoh H, Saito M, Kondo H, Daghlian G, Hong Y-K, Yoshimatsu Y, Hirashima M, Kobashi Y, Okamoto K, Kishimoto T, and Umeda Y. Dose–response relationship of pulmonary disorders by inhalation exposure to cross-linked water-soluble acrylic acid polymers in F344 rats. Part Fibre Toxicol 19: 27. 2022.
22. Yamano S, Takeda T, Goto Y, Hirai S, Furukawa Y, Kikuchi Y, Misumi K, Suzuki M, Takanobu K, Senoh H, Saito M, Kondo H, Kobashi Y, Okamoto K, Kishimoto T, and Umeda Y. Mechanisms of pulmonary disease in F344 rats after workplace-relevant inhalation exposure to cross-linked water-soluble acrylic acid polymers. Respiratory Research 24: 47. 2023.
23. Peake JL, and Pinkerton KE. Chapter 3 - Gross and Subgross Anatomy of Lungs, Pleura, Connective Tissue Septa, Distal Airways, and Structural Units. In: .

Comparative Biology of the Normal Lung (Second Edition). (Parent RA). Academic Press. San Diego. 21–31. 2015.
24. Miller WS. The Lung, Second edition. Charles C Thomas Publisher, Springfield, lll. Charles C Thomas Publisher. Springfield, lll. 1947.
25. Reid L. The Secondary Lobule in the Adult Human Lung, with Special Reference to its Appearance in Bronchograms *. Thorax 13: 110–115. 1958.
26. Tyler NK, Hyde DM, Hendrickx AG, and Plopper CG. Morphogenesis of the respiratory bronchiole in rhesus monkey lungs. Am J Anat 182: 215–223. 1988.
27. Goodarzi M, Azizi S, Koupaei MJ, and Moshkelani S. Pathologic findings of anthraco-silicosis in the lungs of one humped camels (Camelus dromedarius) and its role in the occurrence of pneumonia. Kafkas Universitesi Veteriner Fakultesi Dergisi 2013.
28. Abdel-Salam LR, Hussein FA, Gad MH, Khattal A-RAA, Elhawari WA, Amer AH, and Sheriff DS. LIGHT AND SCANNING MICROSCOPIC STUDIES ON THE TRACHEOBRONCHIAL EPITHELIUM OF THE ONE-HUMPED CAMEL (CAMELUS DROMEDARIUS). Medico Research Chronicles 2: 649–686. 2015.
29. Robinson N, and Furlow P. 1. Anatomy of the Respiratory System. Equine Respiratory Medicine and Surgery 3–17. 2007.
30. Takenaka S, Heini A, Ritter B, and Heyder J. The respiratory bronchiole of beagle dogs: structural characteristics. Toxicology Letters 96–97: 301–308. 1998.
31. Sterner-Kock A, Kock M, Braun R, and Hyde DM. Ozone-induced Epithelial Injury in the Ferret Is Similar to Nonhuman Primates. Am J Respir Crit Care Med 162: 1152–1156. 2000.
32. Colman K, Andrews RN, Atkins H, Boulineau T, Bradley A, Braendli-Baiocco A, Capobianco R, Caudell D, Cline M, Doi T, Ernst R, Esch E van, Everitt J, Fant P, Gruebbel MM, Mecklenburg L, Miller AD, Nikula KJ, Satake S, Schwartz J, Sharma A, Shimoi A, Sobry C, Taylor I, Vemireddi V, Vidal J, Wood C, and Vahle JL. International Harmonization of Nomenclature and Diagnostic Criteria (INHAND): Non-proliferative and Proliferative Lesions of the Non-human Primate (M. fascicularis). Journal of Toxicologic Pathology 34: 1S-182S. 2021.
33. Falcão B, Vieira A, Souza J, Carreiro A, Araújo D, Soares R, Menezes D, and Medeiros G. Lobation and bronchopulmonary segmentation of Callithrix jacchus (Linnaeus, 1758). Biota Neotropica 18 2018.

34. Kennedy AR, Desrosiers A, Terzaghi M, and Little JB. Morphometric and histological analysis of the lungs of Syrian golden hamsters. J Anat 125: 527–553. 1978.
35. Kling MA. A Review of Respiratory System Anatomy, Physiology, and Disease in the Mouse, Rat, Hamster, and Gerbil. Vet Clin North Am Exot Anim Pract 14: 287–337. 2011.
36. Meeusen E, Snibson K, Hirst S, and Bischof R. Sheep as a model species for the study and treatment of human asthma and other respiratory diseases. Drug Discovery Today: Disease Models 6: 101–106. 2009.
37. Wu A, Zheng H, Kraenzle J, Biller A, Vanover CD, Proctor M, Sherwood L, Steffen M, Ng C, Mollura DJ, and Jonsson CB. Ferret Thoracic Anatomy by 2-Deoxy-2-(18F)Fluoro-D-Glucose (18F-FDG) Positron Emission Tomography/Computed Tomography (18F-FDG PET/CT) Imaging. ILAR journal / National Research Council, Institute of Laboratory Animal Resources 53: 9. 2012.
38. Zehtabvar O, Masoudifard M, Rostami A, Akbarein H, Sereshke AHA, Khanamooeiashi M, and Borgheie F. CT anatomy of the lungs, bronchi and trachea in the Mature Guinea pig (cavia porcellus). Vet Med Sci 9: 1179–1193. 2023.
39. Weibel ER. Morphometry of the Human Lung. Springer. Berlin, Heidelberg. 1963.
40. Davies A, and Moores C. Structure of the respiratory system, regard to function. The Respiratory System 11–28. 2010.
41. Jeffery PK, and Li D. Airway mucosa: secretory cells, mucus and mucin genes. European Respiratory Journal 10: 1655–1662. 1997.
42. Miyata R, and Eeden SF van. The innate and adaptive immune response induced by alveolar macrophages exposed to ambient particulate matter. Toxicology and Applied Pharmacology 257: 209–226. 2011.
43. Renne R, Brix A, Harkema J, Herbert R, Kittel B, Lewis D, March T, Nagano K, Pino M, Rittinghausen S, Rosenbruch M, Tellier P, and Wohrmann T. Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. Toxicol Pathol 37: 5S-73S. 2009.
44. Nagano K, Nishizawa T, Umeda Y, Kasai T, Noguchi T, Gotoh K, Ikawa N, Eitaki Y, Kawasumi Y, Yamauchi T, Arito H, and Fukushima S. Inhalation carcinogenicity and chronic toxicity of indium-tin oxide in rats and mice. J Occup Health 53: 175–187. 2011.

45. Umeda Y, Kasai T, Saito M, Kondo H, Toya T, Aiso S, Okuda H, Nishizawa T, and Fukushima S. Two-week Toxicity of Multi-walled Carbon Nanotubes by Whole-body Inhalation Exposure in Rats. J Toxicol Pathol 26: 131–140. 2013.
46. Kasai T, Umeda Y, Ohnishi M, Kondo H, Takeuchi T, Aiso S, Nishizawa T, Matsumoto M, and Fukushima S. Thirteen-week study of toxicity of fiber-like multi-walled carbon nanotubes with whole-body inhalation exposure in rats. Nanotoxicology 9: 413–422. 2015.
47. Kasai T, Umeda Y, Ohnishi M, Mine T, Kondo H, Takeuchi T, Matsumoto M, and Fukushima S. Lung carcinogenicity of inhaled multi-walled carbon nanotube in rats. Part Fibre Toxicol 13: 53. 2016.
48. Yamano S, Takeda T, Goto Y, Hirai S, Furukawa Y, Kikuchi Y, Kasai T, Misumi K, Suzuki M, Takanobu K, Senoh H, Saito M, Kondo H, and Umeda Y. No evidence for carcinogenicity of titanium dioxide nanoparticles in 26-week inhalation study in rasH2 mouse model. Sci Rep 12: 14969. 2022.
49. Yamano S, Goto Y, Takeda T, Hirai S, Furukawa Y, Kikuchi Y, Kasai T, Misumi K, Suzuki M, Takanobu K, Senoh H, Saito M, Kondo H, and Umeda Y. Pulmonary dust foci as rat pneumoconiosis lesion induced by titanium dioxide nanoparticles in 13-week inhalation study. Particle and Fibre Toxicology 19: 58. 2022.
50. Nogueira I, Català M, White AD, Sharpe SA, Bechini J, Prats C, Vilaplana C, and Cardona P-J. Surveillance of Daughter Micronodule Formation Is a Key Factor for Vaccine Evaluation Using Experimental Infection Models of Tuberculosis in Macaques. Pathogens 12: 236. 2023.
51. Kaneko N, Itoh K, Sugiyama A, and Izumi Y. Microminipig, a non-rodent experimental animal optimized for life science research: preface. J Pharmacol Sci 115: 112–114. 2011.
52. Kalita A. Histomorphological Study of the Respiratory System of Mizo Local Pig (zo vawk). Asian Journal of Biomedical and Pharmaceutical Sciences 4 2014.
53. Iwatsuki-Horimoto K, Nakajima N, Shibata M, Takahashi K, Sato Y, Kiso M, Yamayoshi S, Ito M, Enya S, Otake M, Kangawa A, Silva Lopes TJ da, Ito H, Hasegawa H, and Kawaoka Y. The Microminipig as an Animal Model for Influenza A Virus Infection. J Virol 91: e01716-16. 2017.
54. Ramos L, Obregon-Henao A, Henao-Tamayo M, Bowen R, Lunney JK, and Gonzalez-Juarrero M. The minipig as an animal model to study Mycobacterium tuberculosis infection and natural transmission. Tuberculosis (Edinb) 106: 91–98. 2017.

55. Skydsgaard M, Dincer Z, Haschek WM, Helke K, Jacob B, Jacobsen B, Jeppesen G, Kato A, Kawaguchi H, McKeag S, Nelson K, Rittinghausen S, Schaudien D, Vemireddi V, and Wojcinski ZW. International Harmonization of Nomenclature and Diagnostic Criteria (INHAND): Nonproliferative and Proliferative Lesions of the Minipig. Toxicol Pathol 49: 110–228. 2021.
56. Chen P, Hou J, Ding D, Hua X, Yang Z, and Cui L. Lipopolysaccharide-induced inflammation of bronchi and emphysematous changes of pulmonary parenchyma in miniature pigs (Sus scrofa domestica). Lab Anim (NY) 42: 86–91. 2013.
57. Stoltz DA, Meyerholz DK, Pezzulo AA, Ramachandran S, Rogan MP, Davis GJ, Hanfland RA, Wohlford-Lenane C, Dohrn CL, Bartlett JA, Nelson GA, Chang EH, Taft PJ, Ludwig PS, Estin M, Hornick EE, Launspach JL, Samuel M, Rokhlina T, Karp PH, Ostedgaard LS, Uc A, Starner TD, Horswill AR, Brogden KA, Prather RS, Richter SS, Shilyansky J, McCray PB, Zabner J, and Welsh MJ. Cystic Fibrosis Pigs Develop Lung Disease and Exhibit Defective Bacterial Eradication at Birth. Science Translational Medicine 2: 29ra31-29ra31. 2010.
58. Rogers CS, Hao Y, Rokhlina T, Samuel M, Stoltz DA, Li Y, Petroff E, Vermeer DW, Kabel AC, Yan Z, Spate L, Wax D, Murphy CN, Rieke A, Whitworth K, Linville ML, Korte SW, Engelhardt JF, Welsh MJ, and Prather RS. Production of *CFTR*-null and *CFTR-ΔF508* heterozygous pigs by adeno-associated virus–mediated gene targeting and somatic cell nuclear transfer. J Clin Invest 118: 1571–1577. 2008.
59. Semaniakou A, Croll RP, and Chappe V. Animal Models in the Pathophysiology of Cystic Fibrosis. Front. Pharmacol. 9 2019.
60. Yan Z, Stewart ZA, Sinn PL, Olsen JC, Hu J, McCray PB, and Engelhardt JF. Ferret and pig models of cystic fibrosis: prospects and promise for gene therapy. Hum Gene Ther Clin Dev 26: 38–49. 2015.
61. He W, Zhang W, Cheng C, Li J, Wu X, Li M, Chen Z, and Wang W. The distributive and structural characteristics of bronchus-associated lymphoid tissue (BALT) in Bactrian camels (Camelus bactrianus). PeerJ 7: e6571. 2019.
62. Piscitelli MA, Raverty SA, Lillie MA, and Shadwick RE. A review of cetacean lung morphology and mechanics. Journal of Morphology 274: 1425–1440. 2013.
63. Bode G, Clausing P, Gervais F, Loegsted J, Luft J, Nogues V, Sims J, and Steering Group of the RETHINK Project. The utility of the minipig as an animal model in regulatory toxicology. J Pharmacol Toxicol Methods 62: 196–220. 2010.
64. Koch W, Windt H, Walles M, Borlak J, and Clausing P. Inhalation studies with the Göttingen minipig. Inhal Toxicol 13: 249–259. 2001.

65. Windt H, Kock H, Runge F, Hübel U, and Koch W. Particle deposition in the lung of the Göttingen minipig. Inhalation Toxicology 2010.
66. Hewitt RJ, and Lloyd CM. Regulation of immune responses by the airway epithelial cell landscape. Nat Rev Immunol 21: 347–362. 2021.
67. Luecken MD, Zaragosi L-E, Madissoon E, Sikkema L, Firsova AB, De Domenico E, Kümmerle L, Saglam A, Berg M, Gay ACA, Schniering J, Mayr CH, Abalo XM, Larsson L, Sountoulidis A, Teichmann SA, Eunen K van, Koppelman GH, Saeb-Parsy K, Leroy S, Powell P, Sarkans U, Timens W, Lundeberg J, Berge M van den, Nilsson M, Horváth P, Denning J, Papatheodorou I, Schultze JL, Schiller HB, Barbry P, Petoukhov I, Misharin AV, Adcock IM, Papen M von, Theis FJ, Samakovlis C, Meyer KB, and Nawijn MC. The discovAIR project: a roadmap towards the Human Lung Cell Atlas. Eur Respir J 60: 2102057. 2022.
68. Sikkema L, Ramírez-Suástegui C, Strobl DC, Gillett TE, Zappia L, Madissoon E, Markov NS, Zaragosi L-E, Ji Y, Ansari M, Arguel M-J, Apperloo L, Banchero M, Bécavin C, Berg M, Chichelnitskiy E, Chung M, Collin A, Gay ACA, Gote-Schniering J, Hooshiar Kashani B, Inecik K, Jain M, Kapellos TS, Kole TM, Leroy S, Mayr CH, Oliver AJ, Papen M von, Peter L, Taylor CJ, Walzthoeni T, Xu C, Bui LT, De Donno C, Dony L, Faiz A, Guo M, Gutierrez AJ, Heumos L, Huang N, Ibarra IL, Jackson ND, Kadur Lakshminarasimha Murthy P, Lotfollahi M, Tabib T, Talavera-López C, Travaglini KJ, Wilbrey-Clark A, Worlock KB, Yoshida M, Berge M van den, Bossé Y, Desai TJ, Eickelberg O, Kaminski N, Krasnow MA, Lafyatis R, Nikolic MZ, Powell JE, Rajagopal J, Rojas M, Rozenblatt-Rosen O, Seibold MA, Sheppard D, Shepherd DP, Sin DD, Timens W, Tsankov AM, Whitsett J, Xu Y, Banovich NE, Barbry P, Duong TE, Falk CS, Meyer KB, Kropski JA, Pe'er D, Schiller HB, Tata PR, Schultze JL, Teichmann SA, Misharin AV, Nawijn MC, Luecken MD, and Theis FJ. An integrated cell atlas of the lung in health and disease. Nat Med 1–15. 2023.
69. Tsukui T, Wolters PJ, and Sheppard D. Alveolar fibroblast lineage orchestrates lung inflammation and fibrosis. Nature 631: 627–634. 2024.
70. Lin B, Shah VS, Chernoff C, Sun J, Shipkovenska GG, Vinarsky V, Waghray A, Xu J, Leduc AD, Hintschich CA, Surve MV, Xu Y, Capen DE, Villoria J, Dou Z, Hariri LP, and Rajagopal J. Airway hillocks are injury-resistant reservoirs of unique plastic stem cells. Nature 629: 869–877. 2024.
71. Basil MC, Cardenas-Diaz FL, Kathiriya JJ, Morley MP, Carl J, Brumwell AN, Katzen J, Slovik KJ, Babu A, Zhou S, Kremp MM, McCauley KB, Li S, Planer JD, Hussain SS, Liu X, Windmueller R, Ying Y, Stewart KM, Oyster M, Christie

JD, Diamond JM, Engelhardt JF, Cantu E, Rowe SM, Kotton DN, Chapman HA, and Morrisey EE. Human distal airways contain a multipotent secretory cell that can regenerate alveoli. Nature 604: 120–126. 2022.

72. Kadur Lakshminarasimha Murthy P, Sontake V, Tata A, Kobayashi Y, Macadlo L, Okuda K, Conchola AS, Nakano S, Gregory S, Miller LA, Spence JR, Engelhardt JF, Boucher RC, Rock JR, Randell SH, and Tata PR. Human distal lung maps and lineage hierarchies reveal a bipotent progenitor. Nature 604: 111–119. 2022.

Figure legend.

Figure 1.

Macroscopic and microscopic images of the F344 rat lung.

A: Macroscopic overview of a whole rat lung. B: Magnification of the boxed area in panel A. No polygonal pattern can be observed. C: Overall histopathologic view of the left lung. D: High magnification of Fig.1C, showing the boundary between bronchi and alveoli. E: High magnification of Fig.1D.

AD: Alveolar duct; Al: Alveoli; BADJ: bronchiole-alveolar duct junction; TB: Terminal bronchiole.

Figure 2.

Macroscopic and microscopic images of the B6D2F1mouse lung.

A: Macroscopic overview of a whole mouse lung. B: Magnification of the boxed area in panel A. No polygonal pattern can be observed. C: Overall histopathologic view of the left lung. D: High magnification of Fig.2C, showing the boundary between bronchi and alveoli. E: High magnification of Fig.2D.

AD: Alveolar duct; Al: Alveoli; BADJ: bronchiole-alveolar duct junction; TB: Terminal bronchiole.

Figure 3.

Macroscopic and microscopic images of the lung of a naked mole-rat.

A: Overall view of the chest of a naked mole-rat. B: Macroscopic lung structure (right 4 lobes, left 3 lobes). C: Microscopic overall view of the lung. D: High magnification of

Fig.3C, showing the boundary between bronchi and alveoli. E: High magnification of Fig.3D.

AD: Alveolar duct; Al: Alveoli; BR: Bronchiole; TB: Terminal bronchiole.

Figure 4.

Macroscopic and microscopic images of the lung of a capibara.

A: Macroscopic image of the lung. B: Microscopic image of the lung. C: High magnification of Fig.4B, showing the boundary between bronchi and alveoli.

AD: Alveolar duct; Al: Alveoli; RB: Respiratory bronchiole; Arrow: alveoli associated with respiratory bronchioles.

Figure 5.

Macroscopic and microscopic images of the lung of a monkey.

A: Macroscopic image of the lung of cynomolgus monkey. B: Microscopic image of the lung of cynomolgus monkey. C: High magnification of Fig.5B, showing the boundary between bronchi and alveoli. D: High magnification of Fig.5C. E: Macroscopic image of the lung of a common marmoset. F: Microscopic image of the lung of a common marmoset. G: High magnification of Fig.5F, showing the respiratory bronchiole.

AD: Alveolar duct; Al: Alveoli; RB: Respiratory bronchiole; Arrow: alveoli associated with respiratory bronchioles.

Figure 6.

Macroscope images of the lung of a Microminipig.

A: Schematic diagram of the lobular structure and peripheral airways of the pig lung. B: Overall view of the lung. C: High magnification of Fig.6B, showing the polygonal

pattern on the surface of the lung. D: Lung tissue specimen. The red and yellow dotted lines indicate lung lobules.

Ar: Artery; IS: Interlobular septum; RB: Respiratory bronchiole; TB: Terminal bronchiole.

Figure 7.

Microscope images of the lung of a Microminipig.

A: The site of excision when preparing the pathological specimen. B: Microscopic image of the lung specimen, showing very prominent lobular structures and interlobular septa. C: Histology showing distinct lobules surrounded by interlobular septa. D: Interlobular septa composed of interstitium containing lymphatic vessels and veins. E: Respiratory bronchioles. Bronchiolar epithelium and alveoli (arrows) are intermingled. AD: Alveolar duct; Al: Alveoli; IS: Interlobular septum; Ly: Lymphatic vessel; RB: Respiratory bronchiole; TB: Terminal bronchiole; Ve: vein; Arrow: alveoli associated with respiratory bronchioles.

Figure 8.

Macroscopic and microscope images of the lung of a goat.

A: Macroscopic high magnification of a goat's lung, showing a partial polygonal pattern on the surface of the lung. B: Lung tissue specimen. Interlobular septa continuous with the pleura are observed. C: Microscopic image of a lung specimen from a goat. D: High magnification of Fig.8C, showing an interlobular septum continuous with the pleura. E: High magnification of the lung of a goat, showing the boundary between bronchi and alveoli.

Al: Alveoli; IS: Interlobular septum; RB: Respiratory bronchiole; IS: Interlobular septum; Arrow: alveoli associated with respiratory bronchioles.

Figure 9.

Macroscopic and microscope images of the lung of a cow (Holstein).

A: Macroscopic overview of a whole cow lung. B: Magnification of the boxed area in panel A. C: Microscopic image of the lung, showing very prominent lobular structures and interlobular septa. D: High magnification of Fig.9C, showing interlobular septum. E: High magnification of the lung of a cow, showing the boundary between bronchi and alveoli.

AD: Alveolar duct; Al: Alveoli; IS: Interlobular septum; Ly: Lymphatic vessel; RB: Respiratory bronchiole; IS: Interlobular septum; Ve: vein; Arrow: alveoli associated with respiratory bronchioles.

Figure 10.

Microscope images of the lung of a dolphin.

A: Schematic diagram of a terminal respiratory unit of the dolphin lung, with the well-developed Myoelastic sphincters and externally supported Cartilage in the terminal bronchioles, a feature that makes them quite different from other mammals. B: Microscopic image of the lung. C: High magnification of Fig.10B, showing the boundary between bronchi and alveoli. D: High magnification of Fig.10C.

Al: Alveoli; Cl: Cartilage; MES: Myoelastic sphincters; TB: Terminal bronchiole.