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Invited Review

Comparative anatomy of respiratory bronchioles and lobular structures in mammals

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Abstract: Rodents are widely used to study the toxicity of chemicals; however, differences between species indicate that the results from rodents are not always directly transferable to humans. The health of workers exposed to various chemicals and particulates at high doses or for long periods is at risk. Respiratory bronchioles and lobular structures, which are demarcated by interlobular septa, are key sites for occupational lung diseases such as pneumoconiosis; however, 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 in 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, thereby facilitating early disease detection, treatment, and prevention. (DOI: 10.1293/tox.2024-0071; J Toxicol Pathol 2025; 38: 113–129)

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. Several 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 images[5]. Research using genetically modified mice for lung stem cell studies[6–9] has highlighted the anatomical differences between mouse and human lungs[6]. Animals with different lung anatomies may not be appropriate models for human lung diseases. An accurate understanding of lung structure and cellular composition is

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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 or particulates can occur. Workers exposed to high concentrations or for prolonged periods of time to various chemicals are at risk of developing lung diseases, including pneumoconiosis, which is an occupational lung disease caused by the inhalation of dust and fibers. Early symptoms may be absent and not everyone exposed will develop lung lesions, leading to a lack of recognition of the developing disease and resulting in diagnosis only at advanced stages of the dissease[10]. Therefore, appropriate experimental animals are needed for the accurate understanding, early detection, treatment, and prevention of pneumoconiosis and other lung diseases resulting from the 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 forms of pneumoconiosis, are characterized by significant fibrosis of the respiratory bronchioles and alveolar ducts[12–16]. The lymphatic system of the lungs removes inflammatory cells and damaged tissue caused by particulate matter and microorganisms[17], with the subpleural and interlobular lymphatics being the main routes[18]. Computed tomography (CT) imaging of pneumoconiosis often shows small nodules in the 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. Although inorganic dust is known to cause pneumoconiosis, there is no established evidence supporting the effects of organic dust on pneumoconiosis. Therefore, further research on CWAAP-induced disease is required. Workers inhaling CWAAP showed fibrosis in the respiratory bronchioles and pleural and interlobular septal fibrosis[20]. In rats, changes are limited to the alveolar regions, with interstitial fibrosis of the alveolar septa[21, 22]. Although fibrosis was noted, the development of fibrosis and the causative factors may differ between rats and humans, as fibrosis develops in different areas of the lungs 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 studies by Peake and Pinkerton[23], Miller[24], and Reid[25]. Briefly, respiratory bronchioles are defined as the transition zone between the conducting airways and respiratory air spaces[23]. They have structures similar to those of the 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 the lung structure and are bordered by connective tissue septa (interlobular septa). In addition, the interlobular septa extend to the pleura, and under macroscopic observation, they appear as polygonal patterns on the lung surface.

Comparative anatomical studies of respiratory bronchioles and pulmonary lobule structures are crucial for understanding human occupational respiratory diseases. This will also benefit researchers studying human respiratory diseases. However, comprehensive reviews that focus on these structures in different animal species are limited[23]. This review aims to provide an overview of the morphology and function of human respiratory bronchioles and pulmonary lobule structures and to 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 Tables 1 and 2. Gross and histopathological images using H&E-stained slides were observed 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, cynomolgus monkey, and cow lung tissues were provided by Azabu University; beagle dog and cynomolgus monkey tissues were provided by Shin Nippon Biomedical Laboratories, Ltd.; and naked mole-rat lung tissues were provided by Kumamoto University. Whole-slide images of the 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 regarding the presence or absence of respiratory bronchioles and interlobular septa was obtained from published articles (Table 2)[23, 26–31].

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[32]. As these airways branch, their number increases and their diameters decrease. In the peripheral airways, including the respiratory bronchioles, the cross-sectional area and total volume increase dramatically, slowing the airflow until it nearly stops at the periphery[33]. Most airways are lined with pseudostratified ciliated epithelial cells, which decrease in height towards the periphery. The airway mucosa includes goblet, serous, and acinar cells in the submucosal glands[34]. The coordinated activity of cilia and goblet cell secretions forms the mucociliary escalator, which is essential for removing inhaled particles from the lungs. The alveolar epithelium consists mainly 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[35].

Table 1. Presence or Absence of Respiratory Bronchioles and Interlobular Septa in Mammals

Order	Species	Macroscopic image	Microscopic image	
		Polygonal pattern	Interlobular septa	Respiratory bronchioles
Rodents				
	rat (*Rattus norvegicus*)	X	X	X
	mouse (*Mus musculus*)	X	X	X
	naked mole-rat (*Heterocephalus glaber*)	X	X	X
	gray squirrel (*Sciurus carolinensis*)	NA	X	X
	chinchilla (*Chinchilla lanigera*)	X	X	X
	capybara (*Hydrochoerus hydrochaeris*)	X	X	○
Primates				
	cynomolgus monkey (*Macaca fascicularis*)	X	X	◎
	common marmoset (*Callithrix jacchus*)	X	X	◎
	squirrel monkey (*Saimiri sciureus*)	− [a]	X	◎
Cetartiodactyla				
	microminipig (*Sus scrofa domesticus*)	○	◎	○
	domestic pig (*Sus scrofa domesticus*)	○	◎	○
	goat (*Capra Linnaeus*)	○	○	◎
	cow (*Bos taurus*)	○	◎	◎
	reindeer (*Rangifer tarandus*)	○	◎	○
	alpaca (*Vicugna pacos*)	○	○	○
	pantropical spotted dolphin (*Stenella attenuata*)	X	X	X
Perissodactyla				
	donkey (*Equus asinus*)	○	○	− [b]
	black rhinoceros (*Diceros bicornis*)	○	○	− [b]
Carnivora				
	dog (*Canis familiaris*)	X	X	◎
	Bengal tiger (*Panthera tigris tigris*)*	X	X	◎
	Japanese raccoon dog (*Nyctereutes viverrinus viverrinus*)	X	X	◎
	Chinese wolf (*Canis lipus chanco*)	X	X	◎
Marsupialia				
	koala (*Phascolarctos cinereus*)**	X	X	− [b]

◎: Remarkable; ○: Present; X: Absent; −: Unable to determine; NA: Data not available; a: Congestion and hemorrhage; b: Not determine due to unclear bronchiole structure in the prepared specimen. *: Published as a case report; Kuramochi M, Izawa T, Hori M, *et al.* Chordoma of the thoracic vertebrae in a Bengal tiger (Panthera tigris tigris). J Vet Med Sci. 2015 Jul;77(7):893–5. doi: 10.1292/jvms.14-0658. **: Published as a case report; Kuwamura M, Murai F, Nishioka S, *et al.* Late onset cerebellar cortical degeneration in a koala. Aust Vet J. 2009 Aug;87(8):342–4. doi: 10.1111/j.1751-0813.2009.00463.x.

Table 2. Presence or Absence of Respiratory Bronchioles and Interlobular Septa in Mammals from the Literature

Order	Species	Literature information		References
		Lobular septa	Respiratory bronchioles	
Primates				
	human (*Homo sapiens*)	Extensive	1–3 generations	[23]
	rhesus monkey (*Macaca mulatta*)	Few	Several	[23, 26]
Rodents				
	gerbil (*Meriones unguiculatus*)	Few or none	Absent or poorly developed	[23]
	hamster (*Mesocricetus auratus*)	Few or none	Absent or poorly developed	[23]
	guinea pig (*Cavia porcellus*)	Few or none	Absent or poorly developed	[23]
	rabbit (*Oryctolagus cuniculus*)	Few or none	Absent or poorly developed	[23]
Cetartiodactyla				
	camel (*Camelus dromedarius*)	Exist	Present	[27–29]
	sheep (*Ovis aries*)	Extensive	Absent or poorly developed	[23]
Perissodactyla				
	horse (*Equus caballus*)	Extensive	Absent	[30]
Carnivora				
	cat (*Felis catus*)	Few or none	Several	[23]
	ferret (*Mustela putorius furo*)	Few	Several	[23, 31]

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 respiratory bronchioles sites of potential vulnerability in the lung; for example, respiratory bronchioles are a common site for diffuse lung diseases, such as pneumoconiosis. Therefore, studying occupational respiratory diseases in animals without respiratory bronchioles may lead to an underestimation of the impact of inhaled chemicals and particulates in humans.

The interlobular septa, which are connective tissue sheaths extending from the pleura to 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 tissues, thereby keeping the lungs clean. Impairment of this function may lead to the development of lesions. Thickening of the interlobular septa is a common feature in CT images of patients with pneumoconiosis[19]. The presence of lobular structures may have a significant impact on the morphology of lung lesions. Therefore, studying occupational respiratory diseases in animals with lobular structures is crucial for understanding the histopathology of human lung diseases.

This review examined the presence or absence of respiratory bronchioles and lobular structures in the lungs of various experimental and domestic animals. Based on the findings of our research (Table 1) and the existing 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

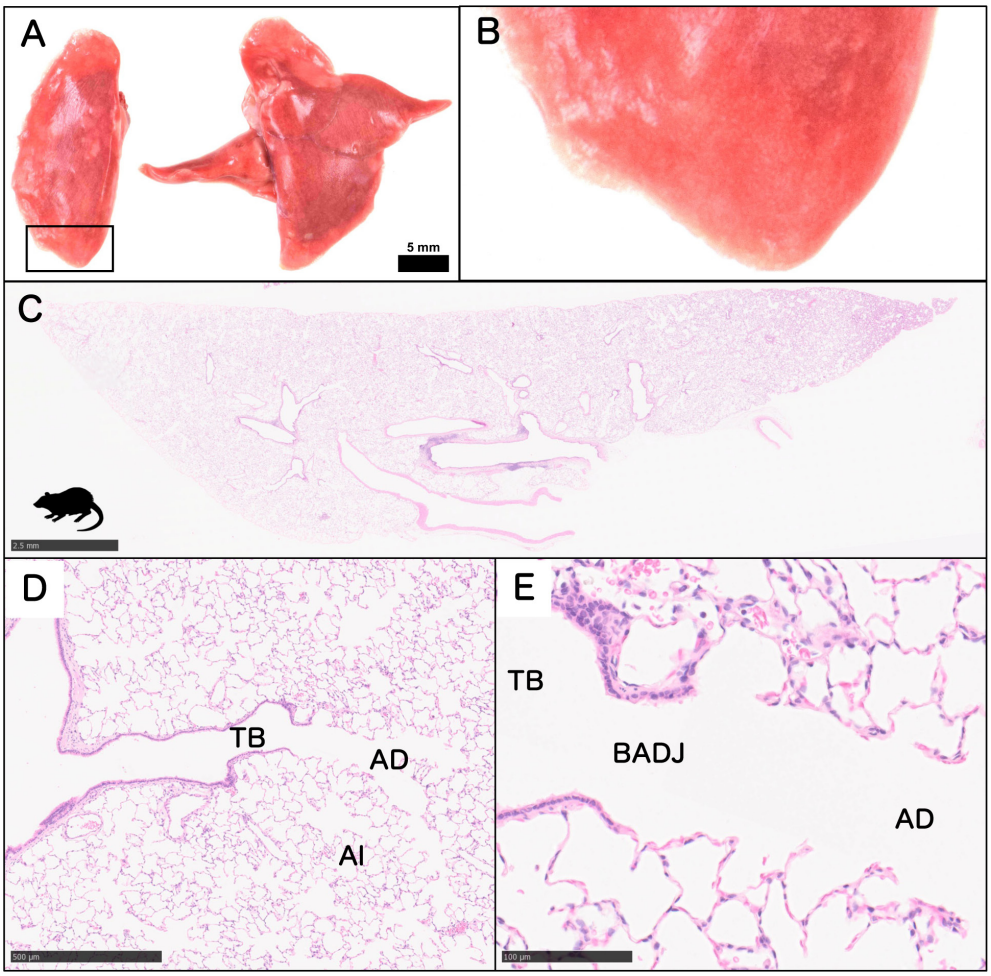

Fig. 1. Macroscopic and microscopic images of the rat lung. A: Macroscopic image of a rat lung. B: Magnified view of the boxed area in panel A. No polygonal patterns can be observed. C: Overall histopathological view of the left lung. D: High-magnification image of Fig. 1C showing the boundary between the bronchioles and alveoli. E: High-magnification image of Fig. 1D. AD: alveolar duct; Al: alveoli; BADJ: bronchiole-alveolar duct junction; TB: terminal bronchiole.

contain respiratory bronchioles or lobular structures. Although human lungs exhibit a polygonal pattern on the surface due to lobular structures, this pattern is absent in rats (Fig. 1A, 1B) and mice (Fig. 2A, 2B). Microscopic examination fails to reveal connective tissue separating the lobules in these rodents (Fig. 1C, Fig. 2C). Therefore, the lobular structures observed in humans are absent in rats and mice. Figures 1 and 2 show the lack of respiratory bronchioles in rats (Fig. 1D, 1E) and mice (Fig. 2D, 2E). Furthermore, their visceral pleura and interstitial connective tissue are relatively thin compared to domestic animals and nonhuman primates[36]. Notably, our inhalation studies with rats and mice using nanomaterials such as indium tin oxide particles[37], multi-walled carbon nanotubes[38–40], and titanium dioxide nanoparticles[41, 42] revealed no interlobular septa lesions or identifiable lobular structure lesions.

To identify rodents with lung structures that are more similar to those of humans, we studied rodents other than rats and mice. In the naked mole-rat (*Heterocephalus glaber*), the longest-living rodent with a lifespan of approximately 30 years, the lung surface does not exhibit a polygonal pattern during gross examination (Fig. 3A). Histological examination also shows no interlobular septa or respiratory bronchioles (Fig. 3B, 3C, and 3D). Similarly, the gray squirrel (*Sciurus carolinensis*) and chinchilla (*Chinchilla lanigera*) (Table 1), gerbil (*Meriones unguiculatus*), hamster (*Mesocricetus auratus*), guinea pig (*Cavia porcellus*), and rabbit (*Oryctolagus cuniculus*)[23] (Table 2) also lack both interlobular septa and respiratory bronchioles. The capybara (*Hydrochoerus hydrochaeris*), the largest rodent with a body weight of 47 kg, also does not exhibit a polygonal pattern or interlobular septa on the lung surface (Fig. 4A, 4B). However, respiratory bronchioles are observed in the capybara, making it the only rodent in this study with such a feature (Table 1, Fig. 4C).

Beagle Dogs and Other Carnivores

In the beagle dog (*Canis lupus familiaris*), which is often used in research, the polygonal pattern observed in

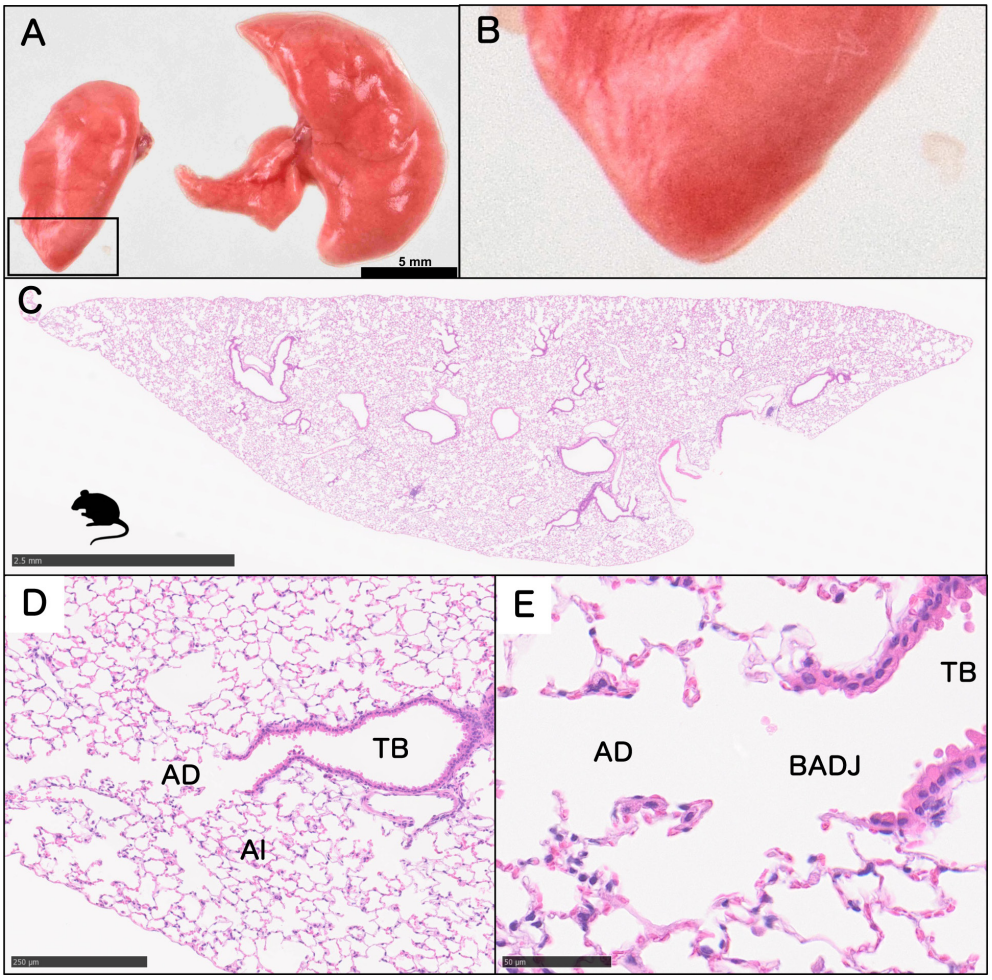

Fig. 2. Macroscopic and microscopic images of the mouse lung. A: Macroscopic image of a mouse lung. B: Magnified view of the boxed area in panel A. No polygonal patterns can be observed. C: Overall histopathological view of the left lung. D: High-magnification image of Fig. 2C showing the boundary between the bronchioles and alveoli. E: High-magnification image of Fig. 2D. AD: alveolar duct; AI: alveoli; BADJ: bronchiole-alveolar duct junction; TB: terminal bronchiole.

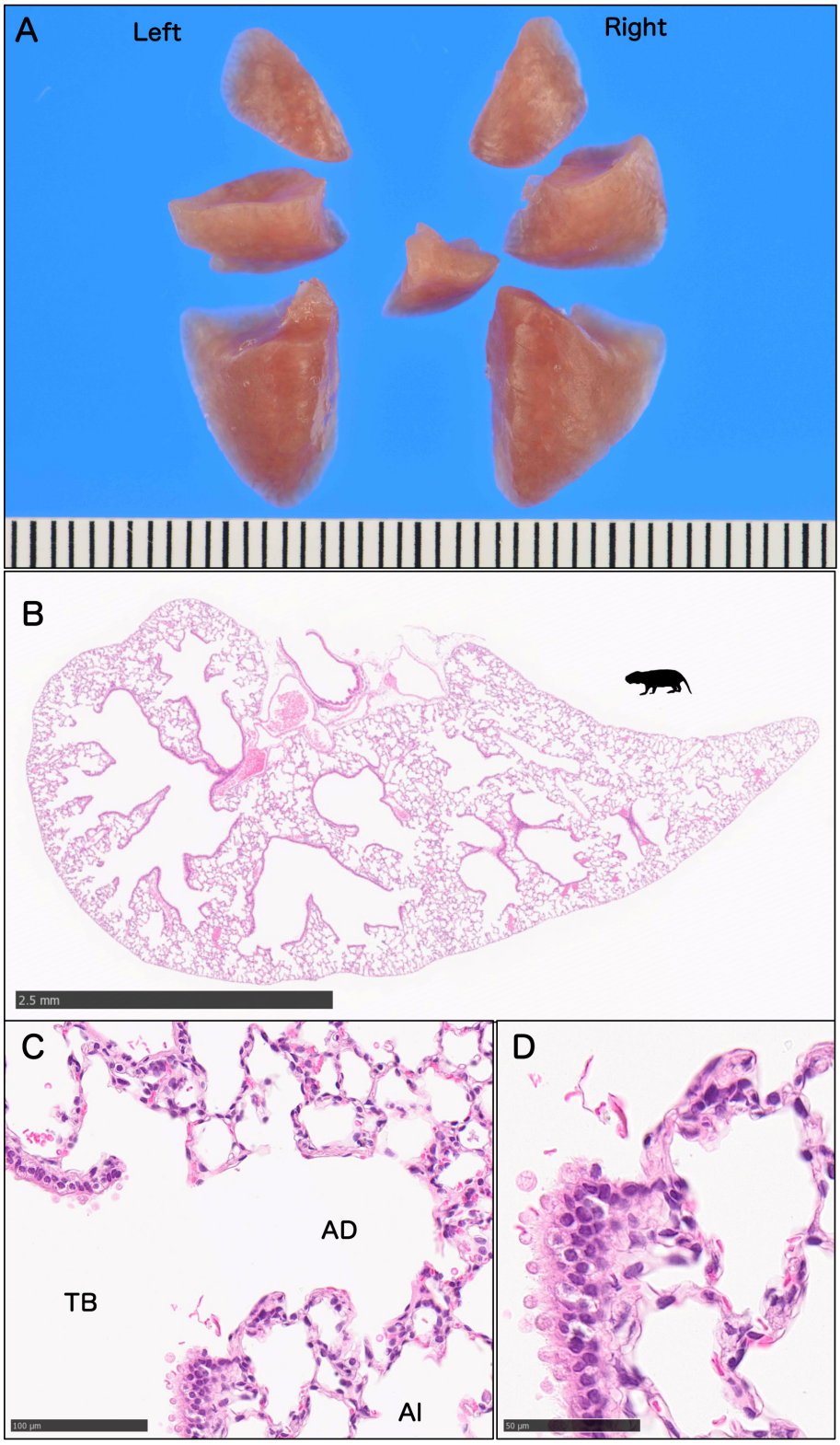

Fig. 3. Macroscopic and microscopic images of the naked mole-rat lung. A: Macroscopic lung structure (left, 3 lobes; right, 4 lobes). B: Microscopic view of the lung. C: High-magnification image of Fig. 3B showing the boundary between the bronchioles and alveoli. D: High-magnification image of Fig. 3C. AD: Alveolar duct; Al: alveoli; TB: terminal bronchiole.

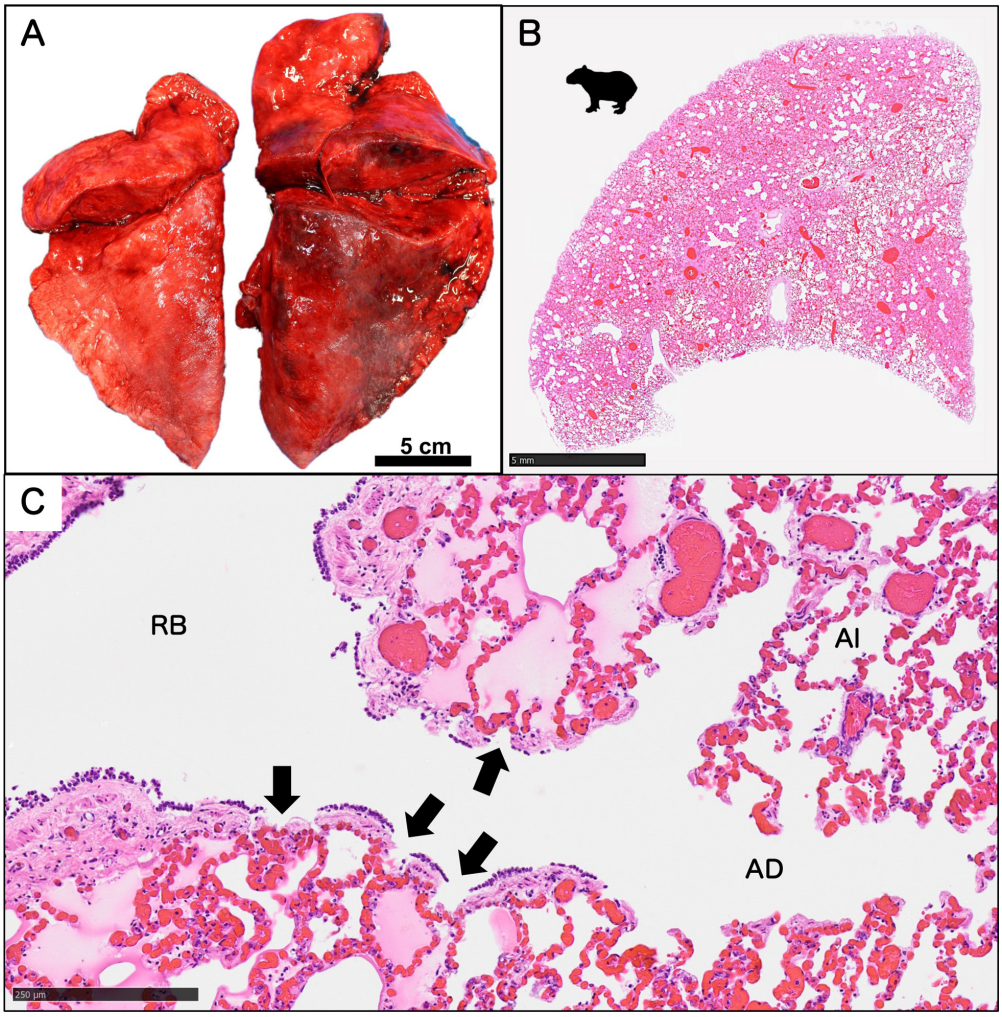

Fig. 4. Macroscopic and microscopic images of the capibara lung. A: Macroscopic image of a capibara lung. B: Microscopic image of the lung. C: High-magnification image of Fig. 4B showing the boundary between the bronchioles and alveoli. AD: alveolar duct; Al: alveoli; RB: respiratory bronchiole; arrow: alveoli associated with respiratory bronchioles.

the human lung is not observed on the surface of the lung (Fig. 5A). Consistent with this finding, the lungs do exhibit any lobular structures (Fig. 5B). However, the respiratory bronchioles are clearly visible (Fig. 5C, 5D; Table 1). Similarly, other members of the order Carnivora, such as Bengal tigers (*Panthera tigris tigris*), Japanese raccoon dogs (*Nyctereutes viverrinus viverrinus*), and Chinese wolves (*Canis lipus chanco*), lack septa but have prominent respiratory bronchioles (Table 1). Notably, cats (*Felis catus*) and ferrets (*Mustela putorius furo*) have respiratory bronchioles but lack interlobular septa, and ferrets in particular are considered to be better models for humans than rodents[23] (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 human peripheral airways; however, as in mice and rats, they lack interlobular septa and are consequently not appropriate models for assessing the effects of the septum on inhalation toxicity and disease.

Nonhuman Primates

In cynomolgus monkeys (*Macaca fascicularis*), a common primate used in research, the polygonal pattern present in human lungs is observed on the lung surface (Fig. 6A). Consistent with this finding, no lobular structures are observed in the lungs (Fig. 6B). However, respiratory bronchioles are clearly visible (Fig. 6C, 6D). The abundant presence of airway smooth muscle tissue in the bronchiolar structure, similar to that in humans, makes it easy to identify the alveolar structure of the respiratory bronchioles. The lung surfaces of the common marmoset (*Callithrix jacchus*) also shows neither a polygonal pattern (Fig. 7A) or microscopic interlobular septa (Fig. 7B). In contrast, respiratory bronchioles are readily visible (Fig. 7C). Similarly, in squirrel monkeys

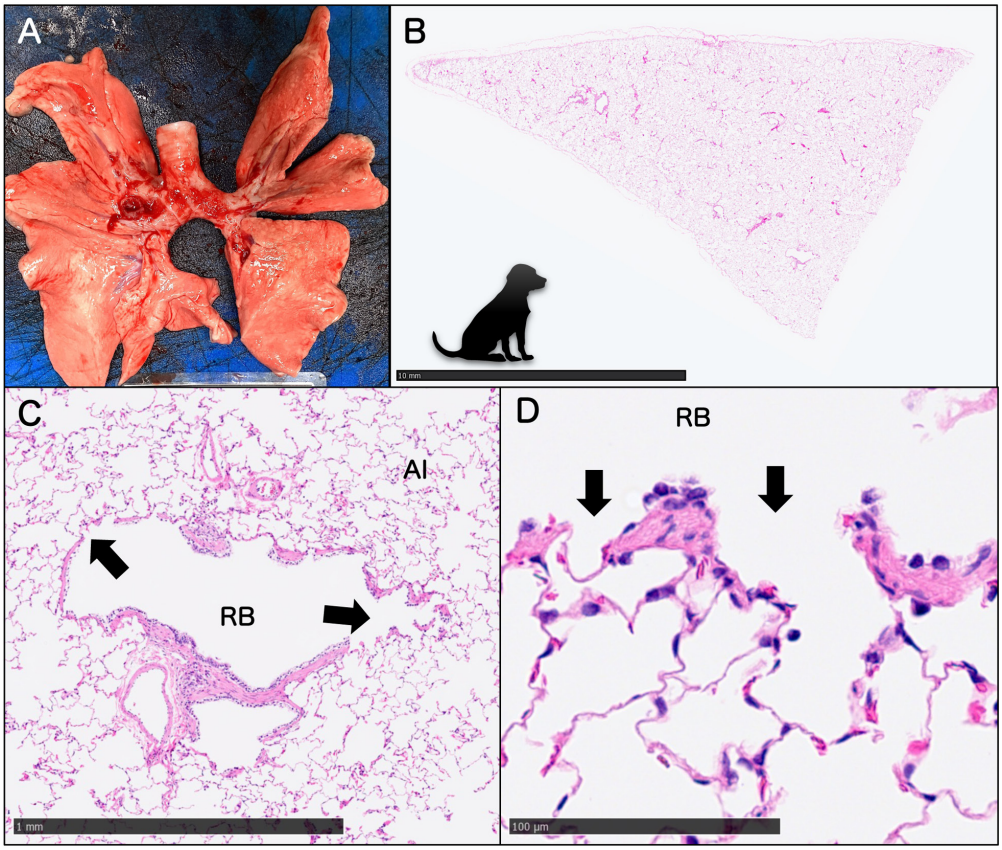

Fig. 5. Macroscopic and microscopic images of the dog lung. A: Macroscopic image of a beagle dog lung. B: Microscopic image of a beagle dog lung. C: High-magnification image of Fig. 5B showing the boundary between the bronchioles and alveoli. D: High-magnification image of Fig. 5C. Al: alveoli; RB: respiratory bronchioles; arrow: alveoli associated with respiratory bronchioles.

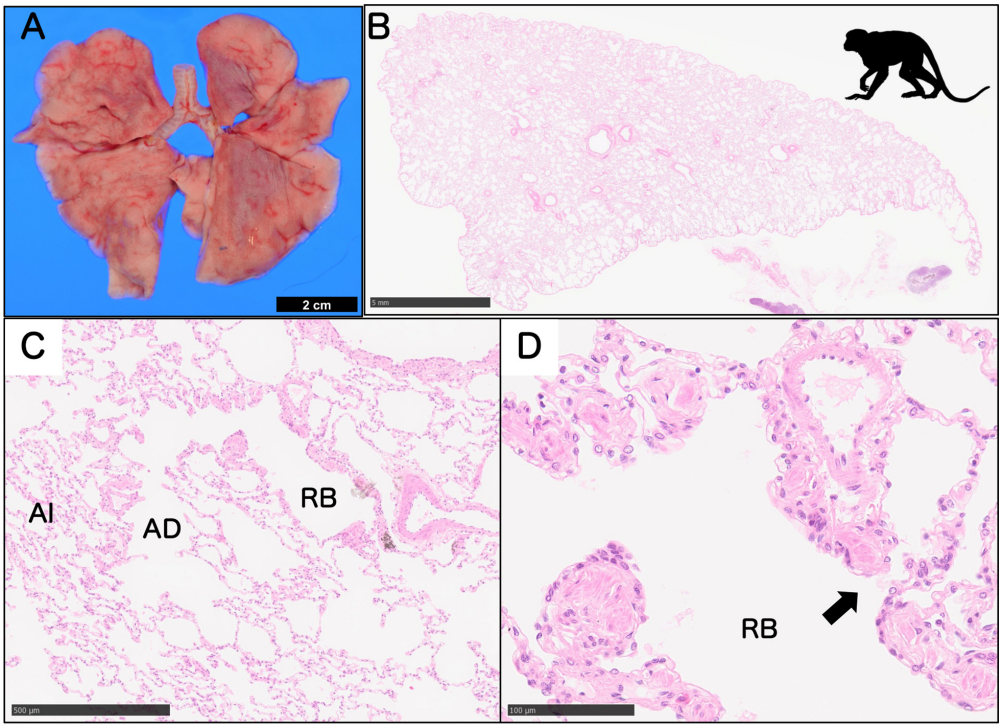

Fig. 6. Macroscopic and microscopic images of the cynomolgus monkey lung. A: Macroscopic image of a cynomolgus monkey lung B: Microscopic image of a cynomolgus monkey lung. C: High-magnification image of Fig. 6B showing the boundary between the bronchioles and alveoli. D: High-magnification image of Fig. 6C. AD: alveolar duct; Al: alveoli; RB: respiratory bronchiole.

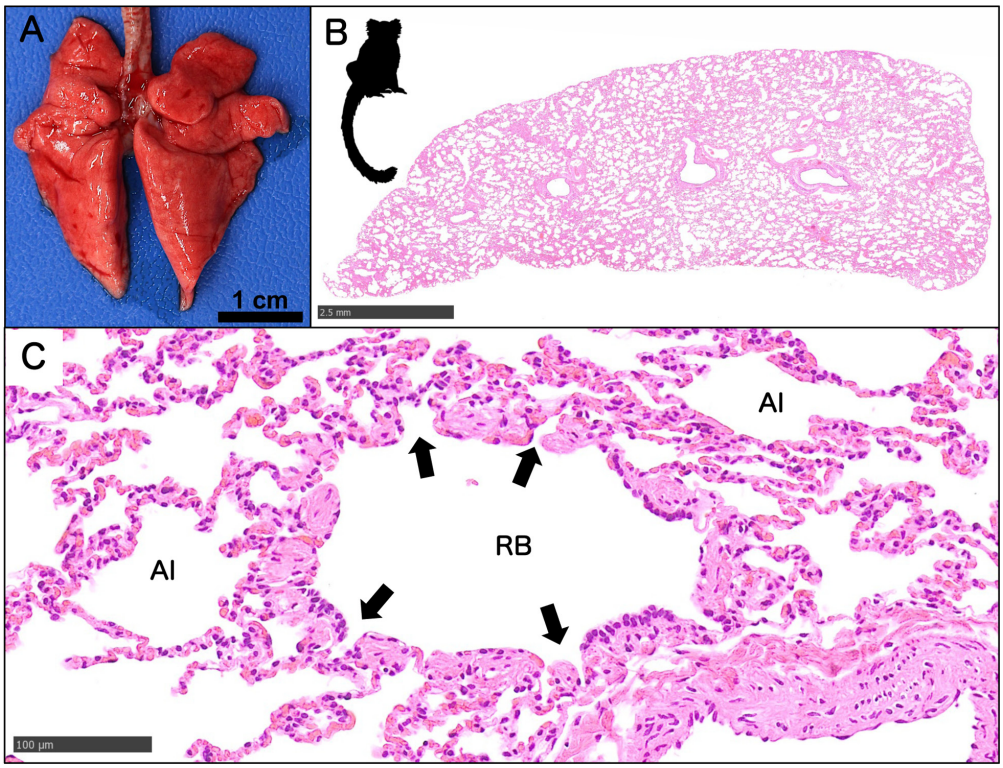

Fig. 7. Macroscopic and microscopic images of the common marmoset lung. A: Macroscopic image of a common marmoset lung. B: Microscopic image of a common marmoset lung. C: High-magnification image of Fig. 7B showing respiratory bronchioles. Al: alveoli; RB: respiratory bronchioles; arrow: alveoli associated with the respiratory bronchioles.

(*Saimiri sciureus*), we observed respiratory bronchioles, but not lobular structures (Table 1). Rhesus monkeys (*Macaca mulatta*)[43], the most commonly 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 were identified between the examined Old World monkeys (cynomolgus monkeys and rhesus monkeys) and New World monkeys (common marmosets and squirrel monkeys). Respiratory bronchioles are observed in both Old World and New World monkeys; however, no clear lobular structures are observed.

Cetartiodactyla

Both respiratory bronchioles and interlobular septa are present in pigs (*Sus scrofa domesticus*) (Table 1). Figure 8A shows the appearance and lobular structure of the pig lung. The Microminipig[44], bred for research, displays a clear polygonal pattern on the lung surface (Fig. 8B, 8C) and well-defined interlobular septa (Fig. 8D). Histologically, the Microminipig lung is partitioned by thin connective tissue and vasculature (Fig. 8E–8I). Distal to the terminal bronchioles, respiratory bronchioles are observed where the bronchiolar epithelium and alveolar epithelium coexist supported by smooth muscle (Fig. 8I). Therefore, unlike rats and mice, pigs have a lung structure similar to that of humans due to their prominent interlobular septa. The Mizo local pig, reared in the Mizoram highlands, has a thick visceral pleura and interlobular septa with elastic fibers, potentially enhancing lung elasticity, and well-developed respiratory bronchioles improving respiratory efficiency[45]. This makes pigs sensitive models for studying diseases involving the interlobular septa.

Goat (*Capra Linnaeus*) lungs also exhibit both respiratory bronchioles and interlobular septa (Table 1). In goat lungs, a partial polygonal pattern is observed (Fig. 9A), and cross-sectional and histopathological examination reveals distinct interlobular septa in continuity with the pleura (Fig. 9C). However, while interlobular septa are present, the pattern of interlobular septa does not appear to be as well developed as in pigs (Fig. 9B). In contrast, respiratory bronchioles are more distinct in goats than in pigs (Fig. 9E).

In the lungs of cows (*Bos taurus*), both respiratory bronchioles and interlobular septa are prominent (Table 1). A polygonal pattern is observed macroscopically (Fig. 10A, 10B), and connective tissue and vasculature define interlobular septa histologically (Fig. 10C, 10D). Respiratory bronchioles with mixed bronchiolar epithelium and alveoli are also observed (Fig. 10E). The lungs of alpacas (*Vicugna pacos*) (Table 1) and camels (*Camelus Linnaeus*)[27, 29], two members of the family Camelidae, also contain both interlobular septa and respiratory bronchioles. Silicosis can develop in camels and, similarly to humans, is associated with diffuse

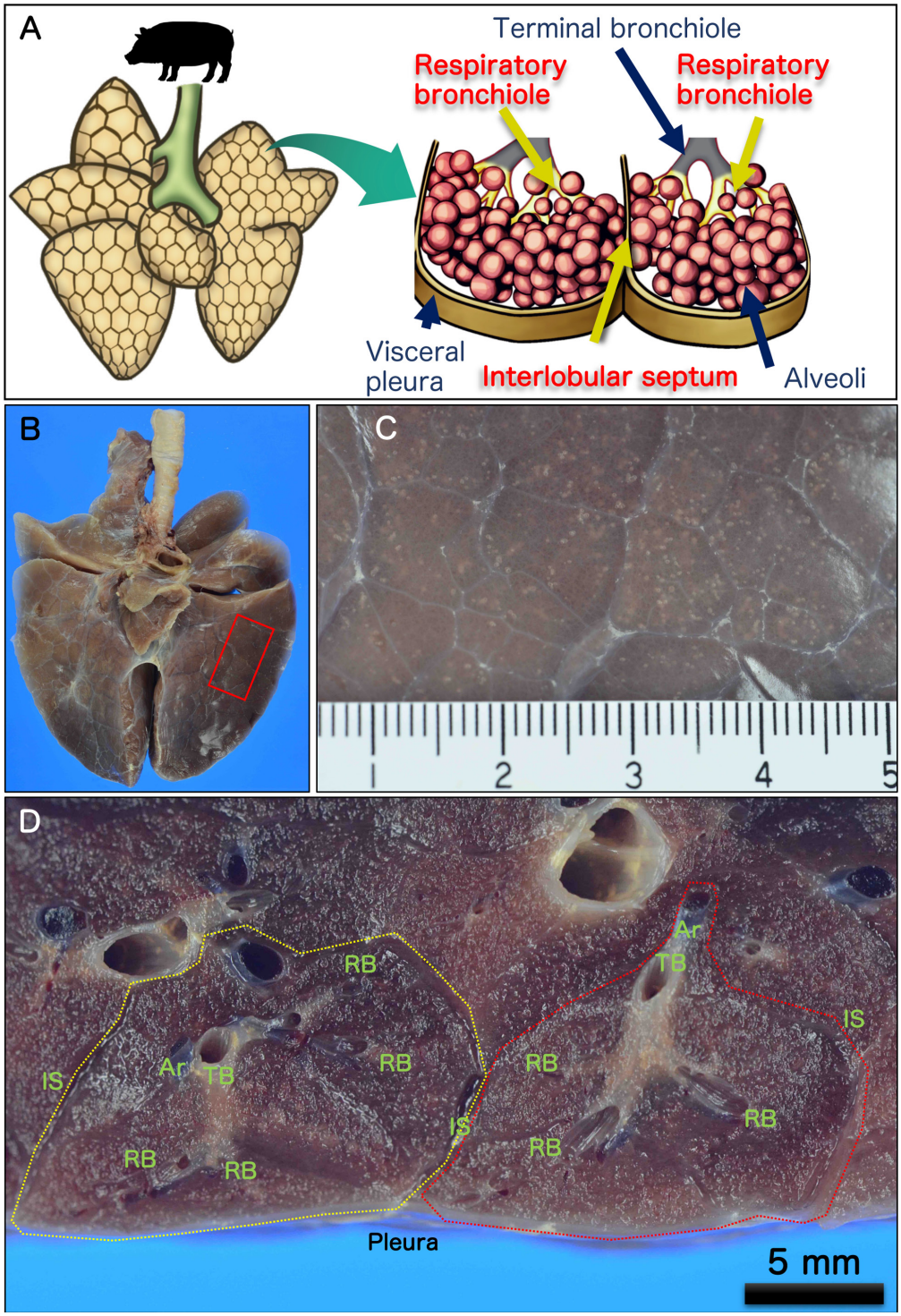

Fig. 8. Continued.

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 reindeer (*Rangifer tarandus*) (Table 1), which belong to the family Cervidae, also possess both interlobular septa and respiratory bronchioles and may be suitable for the study of human occupational respiratory diseases. The lungs of sheep (*Ovis aries*)[23] (Table 2), which belong to the goat subfamily, also have interlobular septa, but unlike goats, respiratory bronchioles are poorly developed.

In contrast, the pantropical spotted dolphin (*Stenella attenuata*), a marine Cetartiodactyla species, does not have respiratory bronchioles or lobular structures and also differs from humans in their bronchial and alveolar structures.

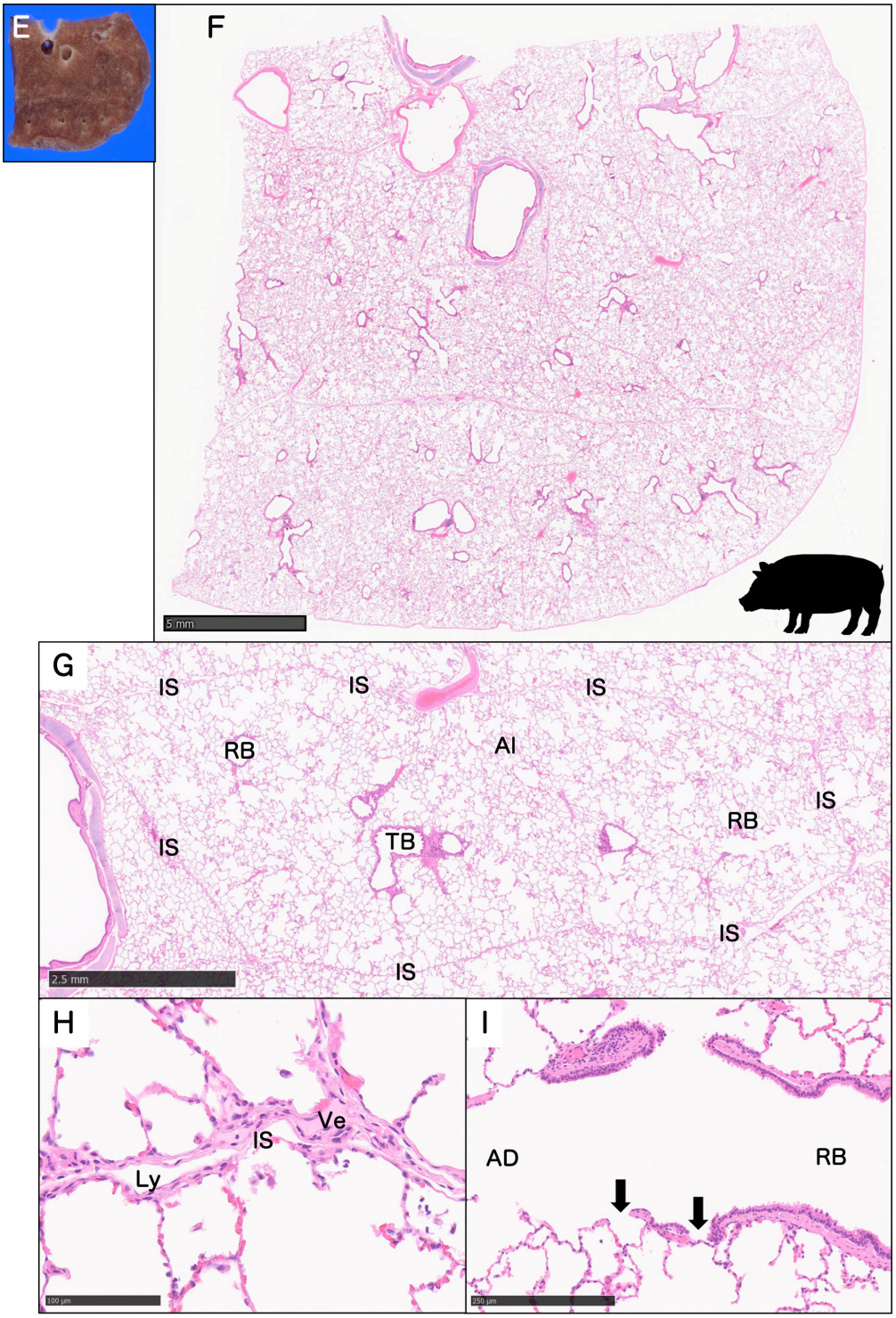

Fig. 8. Macroscope and microscopic images of the Microminipig lung. A: Schematic of the lobular structure and peripheral airways of the pig lung. B: Overall view of the lung. C: High-magnification image of Fig. 8B showing a polygonal pattern on the surface of the lung. D: Lung tissue specimens. The red and yellow dotted lines indicate the lung lobules. E: The site of excision when preparing the pathological specimen. F: Microscopic image of a lung specimen showing prominent lobular structures and interlobular septa. G: Histological image showing distinct lobules surrounded by interlobular septa. H: Interlobular septa composed of interstitium containing lymphatic vessels and veins. I: Respiratory bronchioles. The bronchiolar epithelium and alveoli (arrows) are intermingled. Ar: artery; AD: alveolar duct; Al: alveoli; IS: interlobular septum; Ly: lymphatic vessel; RB: respiratory bronchiole; TB: terminal bronchiole; Ve: vein; arrow: alveoli associated with the respiratory bronchioles.

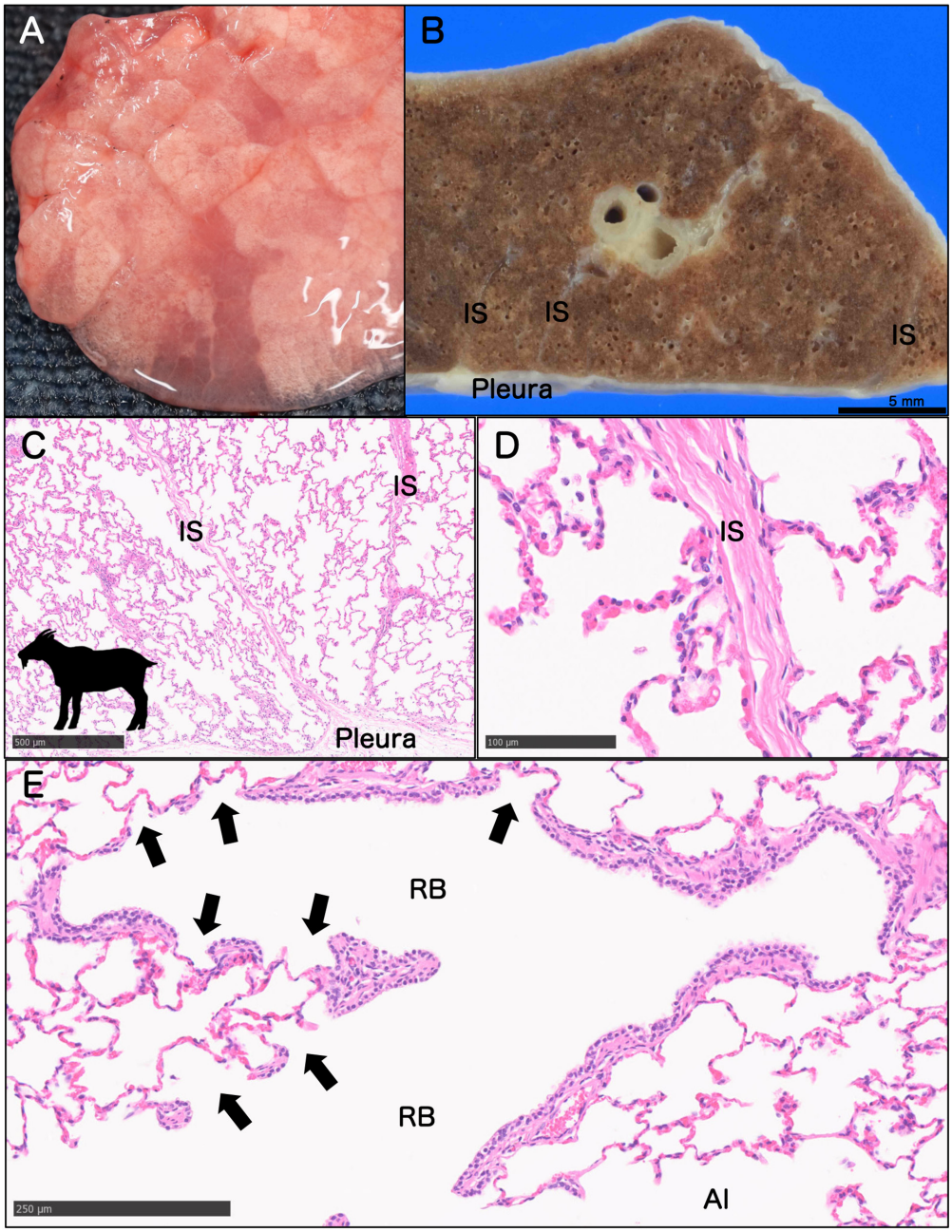

Fig. 9. Macroscopic and microscope images of the goat lung. A: Macroscopic high-magnification image of a goat lung showing a partial polygonal pattern on the lung surface. B: Lung tissue specimen. Interlobular septa continuous with the pleura are observed. C: Microscopic image of a goat lung specimen D: High-magnification image of Fig. 9C showing an interlobular septum continuous with the pleura. E: High magnification image of the lung of a goat showing the boundary between the bronchi and alveoli. Al: alveoli; IS: interlobular septum; RB: respiratory bronchiole; IS: interlobular septum; arrow: alveoli associated with respiratory bronchioles.

The bronchial and lung structure of the dolphin is shown in Fig. 11A. There is no clear lobular structure in dolphin lungs (Fig. 11B), whereas their terminal bronchioles and alveoli are distinct, with cartilage extending to the distal bronchioles (Fig. 11C). Numerous well-developed myoelastic sphincters (MES) formed circular expansions around the terminal bronchiole (Fig. 11C), creating constrictions (Fig. 11C, 11D). Unlike terrestrial species, dolphin alveoli have shallow depressions. This unique structure suggests that the MES regulates airflow, protects the alveoli, and maintains gas exchange in this deep-sea marine species[46].

Other Species

In the order Perissodactyla, both donkeys (*Equus asinus*) and black rhinoceroses (*Diceros bicornis*) show a slight polygonal pattern on the lung surfaces (Table 1). Donkeys and black rhinoceroses have interlobular septa, but not

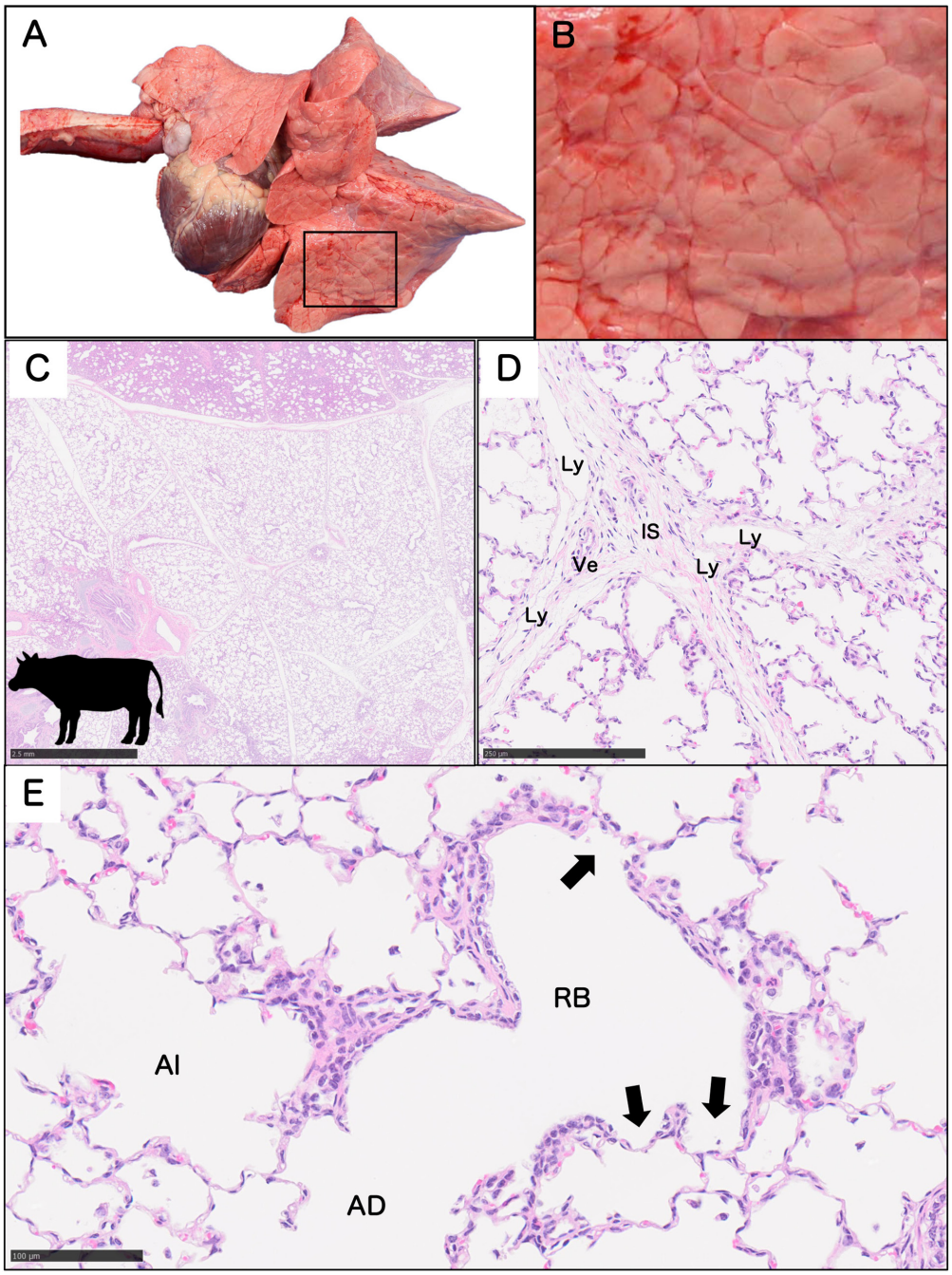

Fig. 10. Macroscopic and microscope images of the cow lung. A: Macroscopic image of a cow lung. B: Magnified view of the boxed area in panel A. C: Microscopic image of the lung showing prominent lobular structures and interlobular septa. D: High-magnification image of Fig. 10C showing the interlobular septum. E: High-magnification image of the lung of a cow showing the boundary between the bronchioles and alveoli. AD: alveolar duct; Al: alveoli; IS: interlobular septum; Ly: lymphatic vessel; RB: respiratory bronchiole; Ve: vein; arrow: alveoli associated with respiratory bronchioles.

as pronounced as in pigs, and respiratory bronchioles can not be resolved due to unclear bronchiole structures. Horses (*Equus caballus*) also have interlobular septa, but with incomplete septal separation of the lobules[30]. In addition, the lungs of horses have been reported to be devoid of respiratory bronchioles (Table 2)[30].

In the order Marsupialia, koalas (*Phascolarctos cinereus*) do not have lobular structures, and the respiratory bronchioles can not be resolved due to unclear bronchiole structures (Table 1).

Discussion and Conclusion

A cross-species investigation of respiratory bronchioles and lobular structures in over 30 mammalian species revealed species variation, with some species having these

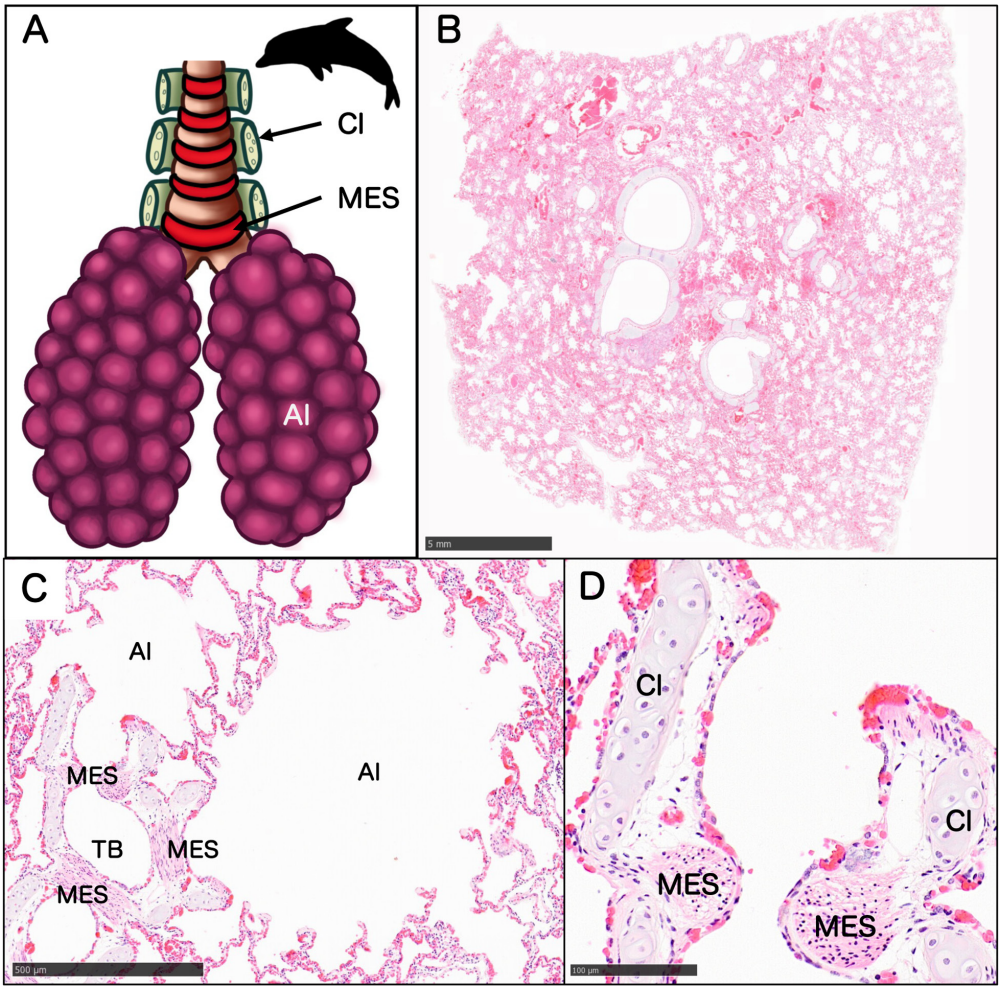

Fig. 11. Microscope images of the dolphin lung. A: Schematic of the terminal respiratory unit of the dolphin lung, with well-developed myoelastic sphincters and externally supported cartilage in the terminal bronchioles, a feature that makes it distinct from other mammals. B: Microscopic image of the lung. C: High-magnification image of Fig. 11B showing the boundary between the bronchiole and alveoli. D: High-magnification image of Fig. 11C. Al: alveoli; Cl: cartilage; MES: myoelastic sphincters; TB: terminal bronchiole.

structures while others did not. None of the rodent species studied exhibit lobular structures. Notably, nonhuman primates show respiratory bronchioles but lack interlobular septa, confirming the absence of human-like lobular structures in these species. Similarly, carnivores show no discernible lobular structures. Therefore, terrestrial even-toed ungulates are reaffirmed as the only animals possessing both respiratory bronchioles and lobular structures, paralleling human respiratory anatomy.

Using pigs, particularly miniature pigs such as minipigs and Microminipigs, can bridge the gap between the results of rodent studies and human clinical studies, enhancing our understanding of respiratory diseases in humans. Minipigs are also used to study infectious diseases[47, 48] and Chronic Obstructive Pulmonary Disease, a leading cause of human mortality[49, 50]. Cystic fibrosis (CF), caused by mutations in the CF transmembrane conductance regulator gene (CFTR), also affects both humans and pigs[51, 52]. In particular, CF studies of the lung using pigs have advantages over studies using mice because of their well-developed submucosal glands[53, 54]. Therefore, 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. 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[55]. In Europe, minipigs are increasingly replacing beagle dogs for safety pharmacology studies[55]. Koch *et al*. at the Fraunhofer Institute in Germany have developed an inhalation model for Göttingen minipigs[56]. This model includes a mask that ensures the precise and reproducible delivery of aerosols and gaseous substances to the airways. They also developed a head-only exposure system and demonstrated the particle-size dependence of lung deposition using a chemical tracer method[57].

Pigs have respiratory bronchioles and lobular structures, making them ideal models for studying occupational respiratory diseases such as pneumoconiosis. In addition to the ethical issues that must be considered when experi-

menting 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 chemical suspensions directly into the lungs of pigs, similar to the intratracheal administration method used in rodents.

This review reconfirms that, aside from humans, only animals belonging to the terrestrial even-toed ungulate taxonomic branch 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 such as silicotic nodules and asbestos lung. The manageable size of miniature pigs and miniature goats makes them suitable for long-term experiments that induce chronic diseases, such as 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 have identified novel cell subsets in the respiratory organs of both healthy and diseased humans, providing new insights into disease pathology[58–62]. Studies have shown that AT0/RAS cells, which are particularly abundant in human respiratory bronchioles, are present in ferrets[63] and monkeys[64], but not in mice, highlighting significant species differences at the single-cell resolution level. We confirmed that these cell subsets are abundant in the lungs of Microminipigs (unpublished data).

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

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