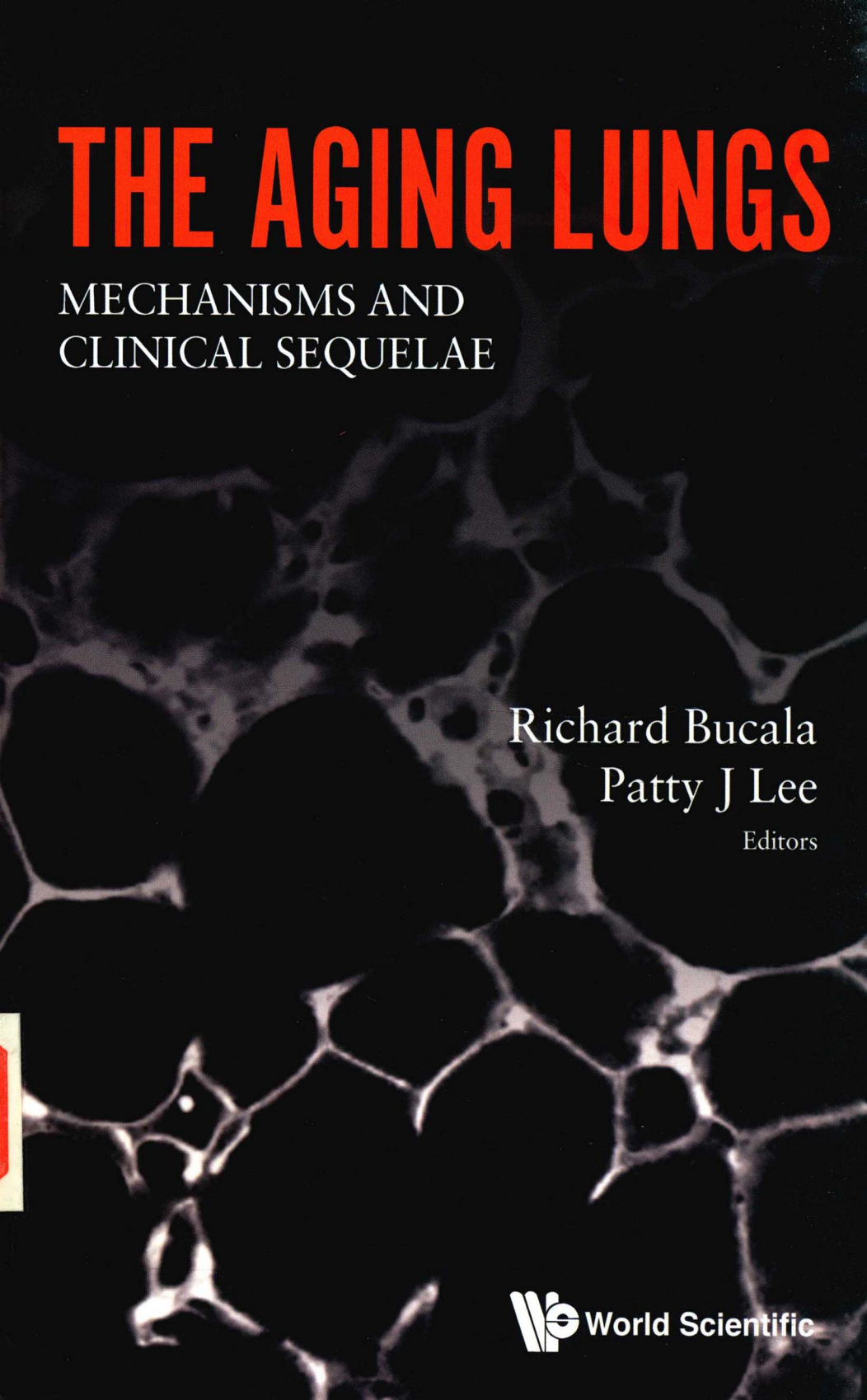
THE AGING LUNGS

MECHANISMS AND CLINICAL SEQUELAE

Richard Bucala
Patty J Lee
Editors



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Accelerated lung aging in a MIF deficient mouse. Photo credit: Maur Sauler, MD.

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Preface

Patty J. Lee and Richard Bucala

> I'm the same person I was back then, A little less hair, a little less chin, A lot less lungs, much less wind. But ain't I lucky I can still breathe in.
>
> *Excerpt from Maya Angelou's 'On Aging'*

The lungs represent the largest interface between the host and the external environment. As a result they have the capacity to mount diverse, complex stress responses but eventually exhibit the cumulative effects of inhaled as well as circulating toxins, antigens and pathogenic microbes. Aging reduces ventilatory capacity and increases vulnerability to stressors, which manifest as increased rates of pulmonary infections, acute respiratory failure and a variety of chronic lung diseases. As the number of Americans over age 65 is estimated to reach 19% of the population, or over 72 million, by 2030, there is urgency in better understanding fundamental mechanisms of lung aging and their clinical manifestations. Dysregulated inflammation, immunosenescence, genomic instability and mitochondrial dysfunction are a few of the emerging theories that link aging and lung disease. This volume will provide a comprehensive overview of the state-of-the-art paradigms in aging lung by leaders in the field.

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Chapter 1

Normal Development, Anatomy, Histology and Aging of the Lung

Xuchen Zhang*,‡ and Robert J. Homer†

1. Introduction

The primary function of the lungs is to exchange gas between air in the external environment and blood in the cardiovascular system. Although this process sounds straightforward, it is fraught with multiple barriers to its success.[1] The entire airway is constantly exposed to the external environment and must cope with challenges including temperature, particles and allergens, toxicants and pathogens. Terrestrial life has adapted to these and other challenges through the evolution of a complex respiratory system consisting of more than 40 different cell lineages.[2,3] The lung's major anatomic components are the airway, including the conducting airways and

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the alveoli; the vasculature, including both pulmonary and systemic circulation; the interstitium, including all supporting tissue, smooth muscle and nerves; the hematopoietic and lymphoid tissues that provide host defense; and finally the poorly understood cells, such as stem (progenitor) cells, perivascular epithelioid cells, meningothelioid cells and others.[2]

The lung is extremely complex not only in structure, with its abundant, diverse cell types in distinct locations, but also in the comprehensive mechanisms of development, maturation, repair and aging processes. The complex nature of lung impacts its normal function, ability to respond to injury and age-associated structural and physiological changes.

2. Lung Development

Mammalian lung development encompasses both prenatal and postnatal life.[4,5] During early embryonic life, the foregut endoderm is specified into domains that will give rise to organs, such as the thyroid, lung, liver and pancreas. Once respiratory cell fate has been established, the tracheal and lung primordial form, which subsequently develops into a tree-like system of epithelial tubules and vascular structures that ultimately becomes the airways and the alveoli. During development the endoderm differentiates into the multiple resident epithelial cell lineages, while the mesoderm will give rise to structures such as the vascular components of the lung, airway smooth muscle, lymphatics, tracheal cartilage, and pleura. Lung development has been extensively studied in recent years, generating new insights into the origins of the different cell lineages that exist in the lung as well as the molecular pathways that regulate these lineages. This has led to novel insights into congenital lung diseases, lung abnormalities and acquired lung diseases, including asthma and chronic obstructive pulmonary disease (COPD), and the lung's response to acute injuries.[1]

2.1. *Lung morphogenesis*

Lung development is essential for terrestrial life and follows a stereotypic program orchestrated by interactions among epithelial

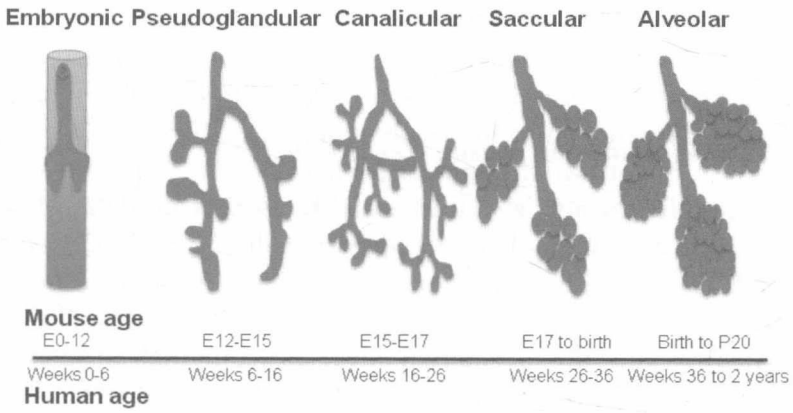

Fig 1. Lung Development. Lung Development in both Mouse and Human Progresses through Five Overlapping Phases: Embryonic, Pseudoglandular, Canalicular, Saccular and Alveolar. E–Embryonic Days, P–Postnatal Days.

and mesenchymal tissues. Lung morphogenesis, together with the trachea, arises from the anterior foregut endoderm, a tissue that generates multiple organs, including the respiratory system, esophagus, thyroid and liver. Typically, lung morphogenesis is divided into five phases (Fig. 1) with some overlap of the beginning and end of each of these phases.[5] It is generally accepted in humans that weeks 0 to 6 of gestation comprise the embryonic phase, weeks 6 to 16 the pseudoglandular phase, weeks 16 to 24 the canalicular phase, weeks 24 to term (40 weeks) the saccular phase, and weeks 36 to 2 years postnatal life the alveolar phase.

2.1.1. *Embryonic phase (Weeks 0 to 6)*

The initiation of lung formation as a bud off the lateral foregut endoderm occurs in the 4th week in humans post conception. During this stage, the trachea completes its separation from the esophagus and branches into the right and left main bronchi and subsequently into lobar and segmental bronchi. Lobar and segmental bronchi appear at about the 5th week and by the end of this stage, 18 major lobules are recognizable. Meanwhile, the bud protrudes into the mesenchyme, which gives rise to the fibroblasts and

vascular cells of the lung as well as to the cartilage and smooth muscle of the airways.

2.1.2. *Pseudoglandular phase (Weeks 6 to 16)*

Pseudoglandular stage is characterized by further branching of airway and vascular network and progressive differentiation of epithelial cells to form adult structures of cartilage, submucosal gland, bronchial smooth muscle and epithelial cell types.[6] By the 7th week, the trachea and the segmental and subsegmental bronchi are evident. By the end of the 16th week, all bronchial divisions are completed. Of note, although the conducting airways will continually enlarge as the fetus and newborn grow (airway diameter and length increase 2–3 folds between birth and adulthood), large airway branching ceases by the end of this phase. Thus, during pseudoglandular phase, all pre-acinar structures, including pre-acinar airway, pulmonary arteries and veins are formed.

2.1.3. *Canalicular phase (Weeks 16 to 26)*

The canalicular phase is marked by completion of the conducting airways through the level of the terminal bronchioles, and the development of the rudimentary gas exchange unit of the lung acinus. The acinus is comprised of a respiratory bronchiole, its associated alveolar ducts and primitive alveoli. Differentiation of type I and type II alveolar cells and formation of the alveolar capillary barrier are established in this canalicular phase. Surfactant protein is detectable by weeks 24 and only by the end of this phase is the fetus able to survive outside the uterus.

2.1.4. *Saccular phase (Weeks 26 to 36)*

By this stage, division of the airways is almost complete and further growth and development of lung structures comprise of enlargement of the peripheral airways with dilatation of acinar tubules forming "saccules" and thinning of the primary septa

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between saccules that contain two layers of capillaries from the neighboring saccules. This ensures increased surface area for gas exchange. There is also further differentiation of type II alveolar cells to type I cells, increment in surfactant containing laminar bodies in type II alveolar cells and lung maturation can be measured by surfactant from amniotic fluid. By the end of this phase (at birth), one third of alveoli are developed. Therefore, the human lung is not fully mature structurally, even at term delivery.

2.1.5. *Alveolar phase (36 weeks to 2 years)*

The alveolar phase is characterized by the presence of secondary septa and the formation of definitive alveoli. Alveoli are formed by septation of the terminal sacs to create more numerous, smaller airspaces in a process termed secondary septation. Alveolar walls are formed by the secondary crests that protrude from the walls of the terminal sacs (primary crests). These secondary septa contain fibroblasts, connective tissue, and two layers of capillaries, and they are covered on either side by epithelium. As with all earlier events in lung development, signaling between the epithelium and mesenchyme is key to coordinating this morphogenesis. As the wall matures, the double layer of capillaries interconnects and eventually fuses to form the single layer present in the adult lung. There are about 50 million alveoli in the lungs of the full-term infant, which provide sufficient gas exchange for the beginning of extra-uterine life. Postnatal, alveoli continue to grow in size and number by septation, until the child reaches 2–3 years of age. Some alveoli may continue to be developed up to 8–10 years of age. The final numbers of alveoli in the fully developed lung range from 300–600 million with a total surface area of about 70 m^2, which is approximately 1000 alveoli per acinus.

3. Mechanisms of Lung Development

During the lung morphogenesis, separation of the tracheal tube from the esophagus and formation of the branching lung are the

two major developmental processes. The understanding of these basic lung developmental processes has significantly improved through extensive studies in mouse molecular genetics and genomics. It is well recognized that these developmental processes are regulated by diverse signaling crosstalk between the epithelial cells and surrounding mesenchyme, which are highly coordinated by growth factors, transcriptional factors, and extracellular matrix residing in the lung microenvironment. In addition, a number of epigenetic regulators and non-coding RNAs have been identified as key regulators of lung development.[4,7] A full review of signaling pathways involved in lung morphogenesis is beyond the scope of this chapter, but the best-established pathways will be briefly discussed.

3.1. *Specification of the lung endoderm from the anterior foregut*

The first and most important transcription factor in the lung specification from the anterior foregut endoderm is thyroid transcription factor-1 (TTF-1), a product of the *NKX2.1* gene. Expression of the transcription factor TTF-1 occurs at about embroyal (E) day 9.0 in the mouse and 4 weeks gestation in the human. TTF-1 is considered a master regulator of specification of the lung endoderm in the anterior foregut, as *NKX2.1* null mice exhibit absence of lung specification by showing markedly foreshortened trachea that remains fused to the esophagus, resembling a relatively rare anatomical deformity in humans, known as 'complete tracheo-esophageal cleft'. Studies have shown that Wnt signaling pathway plays a crucial role in specifying *NKX*2.1+ respiratory endoderm progenitors during development. Wnt2 and Wnt2b are expressed in the ventral anterior mesoderm surrounding the region of the anterior foregut endoderm where *NKX*2.1+ respiratory endoderm progenitors are located.[8] In Wnt2/2b combined null mutants, embryos lacking Wnt2/2b expression exhibit complete lung agenesis and do not express *NKX*2.1.[8] This phenotype is recapitulated by an endoderm-restricted deletion of β-catenin.[8,9] On the contrary, conditional expression of an activated form of β-catenin leads to an expansion

of *NKX*2.1+ progenitors in the posterior gut, including the stomach, suggesting that Wnt is not only necessary but also sufficient to drive lung progenitor identity in foregut endoderm.[8,9] Wnt signaling does not act alone in specifying lung fate; the ability of Wnt/β-catenin signaling to promote *NKX*2.1+ respiratory endoderm progenitor fate is dependent upon other associated signaling pathways, such as active bone morphogenetic protein (BMP) signaling.[10] Bmp4 is expressed in the ventral mesenchyme surrounding the anterior foregut, and loss of Bmp signaling in the foregut endoderm through inactivation of the BMP receptors Bmpr1a and Bmpr1b leads to tracheal agenesis with retention of the branching region of the lungs. Bmp signaling appears to act by repressing the transcription factor SRY-box containing gene 2 (SOX2), which allows for expression of *NKX*2.1 in the presumptive lung endoderm.[10,11] Thus, both Wnt and Bmp signaling appear to modulate early lung specification and development.

3.2. *Branching morphogenesis and epithelial differentiation of the lung*

After the early budding of the main bronchi or airways, the lung buds extend into the surrounding mesenchyme and develop rapidly through a process called branching morphogenesis. Branching morphogenesis is essential for forming both the structural airways as well as the terminal alveolar compartments in which gas exchange occurs.[1] Although the exact mechanisms are still unclear, several pathways have been found to be involved in the branching morphogenesis process. Fibroblast growth factor (FGF) signaling, in particular FGF10 signaling to its cognate receptor FGFr2 in the developing endoderm, is essential for branching morphogenesis, and loss of this pathway leads to complete abrogation of branching.[12,13] FGF10 is one of the most-studied family members during lung development. FGF10-null mice lack distal lung despite formation of larynx and trachea is normal.[14] FGF10 is expressed focally in E11–E12 mouse peripheral lung mesenchyme and signals through adjacent distal epithelial FGFr2. These sites of expression change dynamically,

compatible with the sites of lung bud formation. Several key regulatory molecules such as Wnt, sonic hedgehog (Shh), BMPs, and TGF-β crosstalk with FGF10 during embryonic lung branching morphogenesis, suggesting a complex interplay of signaling molecules.[15–17]

During branching morphogenesis, the lung endoderm also begins to develop distinct cell lineages along its proximal-distal axis. SOX2 expression marks the proximal endoderm progenitor lineage whereas the combined expression of Sox9 and the transcriptional regulator inhibitor of DNA binding 2 (ID2) marks the distal endoderm progenitor lineage. Importantly, these two populations have distinct fates: The proximal progenitors give rise to airway neuroendocrine cells, secretory cells, ciliated cells and mucosal cells, whereas the distal progenitors give rise to type 1 and type 2 alveolar epithelial cells.[1] Studies have shown that SOX2 is necessary for the differentiation of proximal progenitors into their various progeny; loss of SOX2 expression leads to loss of the mature secretory and ciliated lineages in the lung airways.[18,19] The precise molecular pathways required for the formation and differentiation of distal SOX9/Id2 progenitors are poorly understood. Inhibition of both Wnt/β-catenin signaling and BMP signaling results in a loss of distal lung epithelial lineages.[20–22] In addition, transcription factors, such as NKX2.1 and forkhead box (Foxp1/2), appear to play important roles in the differentiation of distal endoderm progenitors.[23,24]

TTF-1, regulator of lung specification from the anterior foregut, also has a prominent role in establishing cell fate along the proximal to distal lung epithelium. TTF-1 expression continues to be expressed by epithelial cells at the distal tips of the branching lung epithelium, ultimately becoming more restricted to Clara cells and alveolar type 2 cells. TTF-1 is critical for the expression of genes that are unique to differentiated epithelium, such as CC10 expression in Clara cells and sftp in alveolar type 2 cells. DNA binding sites for TTF-1 are found in the promoter regions of all four surfactant proteins (sftp a-d), CC10, and *NKX2.1* itself, creating a positive feedback loop for sustained TTF-1 expression. Furthermore, *NKX2.1* expression can itself interact with additional transcriptional regulators such as Gata-6 and Foxa2.[25,26] Gata-6 is a member of the Gata

family of zinc finger proteins and is expressed in endodermally derived tissues including the lung.[27] GATA-6 and NKX2.1 directly interact and regulate sftp-C gene expression.[27] Mice heterozygous for both Gata-6 and *NKX*2.1 have defects in lung epithelial cell differentiation.[28] The Fox family proteins, Foxa1 (also known as hepatocyte nuclear factor-3, Hnf-3α) and Foxa2 (also known as Hnf-3β), are key regulators of endoderm identity and development. The combined loss of Foxa1 and Foxa2 leads to severe defects in lung epithelial cell differentiation, including loss of the alveolar type 2 cell markers (Sftpc and Sftpb) and the airway epithelial markers for the secretory (secretoglobin 1A member 1, Scgb1a1) and ciliated (Foxj1) epithelial lineages.[29] Both Foxa1 and Foxa2 regulate the expression of *NKX*2.1, which in turn regulates transcription of the sftp genes in lung epithelial cells.[26,30] Other Fox transcription factors, such as Foxj1, which is required for differentiation of proximal SOX2+ progenitors into ciliated epithelium, and overexpression of Foxj1 throughout the developing lung epithelium leads to ectopic formation of ciliated epithelium.[31–33] Foxp1, Foxp2 and Foxp4 are highly expressed in the developing and postnatal lung; Foxp1 and Foxp4 are expressed in both proximal and distal epithelial lineages while Foxp2 is expressed primarily in distal epithelium. Loss of Foxp2 in mouse leads to defective postnatal lung alveolarization and death, 3 weeks after birth.[24] When the lung alveolus is formed, Foxp2 modulates the *NKX*2.1-mediated sftp C expression in type II alveolar cells.[34]

4. Lung Anatomy and Histology

The lungs are paired intrathoracic organs that are divided into 5 lobes (3 on the right-upper, middle and lower lobes; two on the left-upper and lower lobes), and the lobes are further divided into bronchopulmonary segments. The segmental anatomy of the lung is important for radiologists, bronchoscopists, pathologists and thoracic surgeons in accurately defining the location of lesions and performing the segmentectomy procedures.[35] The lingula is a rudimentary appendage arising from the left upper lobe and is analogous to the middle

lobe on the right. The right lung usually weighs about 625 gm and the left 567 gm, but much variation is met with according to the amount of blood or serous fluid they may contain. The lungs are heavier in the male than in the female. Increased lung weight can be an indication of congestion, edema, or inflammatory conditions. The right main bronchus is more vertical and more directly in line with the trachea than is the left. Consequently, aspirated foreign material, such as vomitus, blood and foreign bodies, tend to enter the right lung rather than the left.

The lung and all surfaces connected to the lung including diaphragm, mediastinum and inner chest wall are covered by a serosal surface lined by mesothelial cells. The visceral and parietal pleurae are continuous with each other around the hilar structures. The potential space between them is the pleural cavity, which is maintained at a negative pressure by the inward elastic recoil of the lung and the outward pull of the chest wall. It contains a small amount of fluid that allows for smooth, friction free movement of the lung. However, the entry of air or the accumulation of fluid in the pleural cavity may lead to mechanical dysfunction of breathing.[36] Thoracoscopy allows the direct inspection of both the parietal and visceral surfaces. The parietal pleura is translucent and at thoracoscopy the underlying muscles and blood vessels are visible. The visceral pleura is also translucent and has a grey variegated appearance due to the underlying lung and the vascular network in the subpleural layer.

The muscles of respiration and the diaphragm, acting together, create a negative pressure within the pleural space. The resultant reduction in intra-alveolar pressure prompts the conduction of air through the upper respiratory tract into the trachea and airways and then into the alveoli, where gaseous exchange occurs. The respiratory muscles are skeletal muscles similar to the skeletal muscles of the limbs. However, certain functions of respiratory muscles are distinct. They must work without sustained rest throughout life and as a result have high oxidative capacity with increased numbers of mitochondria, high capillary density and greater maximal blood flow than other skeletal muscles. The fiber type distribution in respiratory

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