



HISTOPHYSIOLOGY OF THE ACINUS. LUNG REGENERATION AND TRANSPLANTATION

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Abstract

This article provides a detailed examination of the histological structure, cellular composition, and histophysiological characteristics of the acinus—the primary structural and functional unit of the lung. It analyzes the roles of alveolar epithelium (type I and type II alveolar epithelial cells), capillary endothelium, the interstitium, and alveolar macrophages in processes such as gas exchange, surfactant synthesis, fluid balance, and local defense mechanisms. Furthermore, the article explores the physiological renewal of lung tissue and the mechanisms of regeneration following injury—involving type II alveolar epithelial cells, basal cells, bronchoalveolar stem cells, and regenerative niches—as well as the consequences of impaired regeneration (such as fibrosis and emphysema). It also addresses the histological and immunological foundations of lung transplantation, potential complications, and contemporary developments in the field, including *ex vivo* perfusion, bioengineering, organoids, and xenotransplantation.

Keywords: acinus, alveolus, type II alveolar epithelial cell, surfactant, air-blood barrier, lung regeneration, stem cells, lung transplantation, rejection reaction, CLAD.

Introduction

The primary function of the respiratory system is to facilitate gas exchange between the organism and the external environment. This process takes place in the acinus—the most distal unit of the lung. The human adult lung contains approximately 480 million alveoli (with individual variation ranging from roughly 270 to 790 million), providing a total respiratory surface area estimated at 130–140 m² [1, 2]. This extensive surface area enables gas diffusion between the air and the blood across an extremely thin barrier (averaging 0.5–0.6 μm). Consequently, any disruption to the structure of the acinus—whether through inflammation, fibrosis, emphysema, or ischemic injury—directly leads to respiratory failure.



Because lung tissue is in constant contact with the external environment, it is frequently exposed to dust, microorganisms, toxins, and viruses. Despite this, the pulmonary epithelium exhibits a slower turnover rate compared to many other mammalian tissues (with cellular replacement in the alveolar epithelium occurring over months or years); however, it demonstrates a remarkable capacity for regeneration following injury. Over the past 15 years, advances in single-cell transcriptomics, lineage tracing, and organoid technologies have fundamentally transformed our understanding of lung regeneration.

In end-stage pulmonary diseases (chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, cystic fibrosis, and pulmonary arterial hypertension)—where the potential for regeneration has been exhausted—lung transplantation remains the only effective treatment. However, the scarcity of donor organs, primary graft dysfunction, and chronic lung allograft dysfunction (CLAD) limit the outcomes of transplantation. Consequently, studying the histophysiology of the acinus, the mechanisms of regeneration, and the histopathology of transplantation within a unified framework holds both theoretical and practical significance.

The objective of this article is to provide a systematic overview of the histological structure and physiological functions of the acinus, the cellular and molecular foundations of pulmonary regeneration, and the morphological and clinical aspects of transplantation.

1. Morphological Structure of the Acinus

1.1. Structural-Functional Units of the Lung

The pulmonary parenchyma is composed of units organized into several hierarchical levels. These include:

- Segment — a portion of the lung supplied by a segmental bronchus and its accompanying artery, bounded by connective tissue septa (there are 8–10 in each lung).
- Secondary pulmonary lobule (Miller's lobule) — a region supplied by a lobular bronchiole and surrounded by interlobular septa; it measures approximately 1–2.5 cm and may contain 3–5 terminal bronchioles. In radiology, this is the smallest anatomical unit visible on a CT scan.
- Acinus (Latin for "grape-like cluster") — the entire collection of structures supplied with air by a terminal bronchiole that participate in gas exchange. It is considered the true gas-exchange unit of the lung.

1. The concept of the acinus has been in use since the time of Malpighi; its modern morphometric description was provided by E. Weibel and colleagues [1, 7]. The human lung contains approximately 14,000 acini, with each acinus estimated to have an average volume of 150–200 mm³ (though this varies significantly between individual acini).

1.2. Structure of the Acinus



The acinus begins at the transition from the terminal bronchiole and consists of the following components:

1. Respiratory bronchioles (*bronchioli respiratorii*) — of the 1st to 3rd order; their walls contain openings for alveoli, and they function as a transitional zone. Proximally, the epithelium consists of cuboidal, ciliated, and Club cells, transitioning distally into a flat (squamous) alveolar epithelium.
2. Alveolar ducts (*ductus alveolares*) — the walls of which consist almost entirely of the openings of alveoli; between these openings, ring-like bundles of smooth muscle fibers (alveolar "knots" or septal tips) are present.
3. Alveolar sacs (*sacculi alveolares*) — the expanded, blind-ending terminal portions of the alveolar ducts.
4. Alveoli — thin-walled, hemispherical sacs; the smallest gas-exchanging units of the lung..

In the Weibel model, the trachea represents generation 0; terminal bronchioles in humans correspond approximately to generations 14–16, while the acinus occupies the range of approximately generations 17–23 (roughly 6–8 dichotomous divisions). Over this distance, air transport occurs primarily via diffusion: convection dominates at the entrance to the acinus, while diffusion becomes the prevailing mechanism distally (the "stationary front" concept).

- The size of an alveolus varies depending on the phase of respiration: the average diameter is 200–250 μm (shrinking to 150–200 μm at the end of expiration, and potentially exceeding 300 μm during full inspiration). Between adjacent alveoli, there are pores of Kohn (3–13 μm), which facilitate collateral ventilation. Channels of Lambert also exist between bronchioles and alveoli. While these pathways help maintain some airflow in the event of bronchial obstruction, they also provide a route for the spread of infection and exudate.

1.3. The Alveolar Wall and the Air-Blood Barrier

The interalveolar septum (*septa interalveolaris*) consists of the following layers:

- alveolar epithelium (type I and type II alveolocytes) and its basement membrane;
- interstitial space (virtually absent in the thin segment; contains elastic and collagen fibers, fibroblasts, pericytes, mast cells, and lymphocytes in the thick segment);
- capillary endothelium and its basal membrane.

In the thin (gas-exchange) region, where gas exchange occurs, the basal membranes of the epithelium and endothelium fuse to form a single layer 0.1–0.2 μm thick; in the thick (structural/supportive) region, interstitial tissue is present, which facilitates fluid exchange and provides mechanical support. The total average thickness of the air-blood barrier (comprising the surfactant film, the cytoplasm of type I alveolar cells, the fused basal membrane, and the endothelial cytoplasm) is 0.2–0.6 μm in the thin regions.

The alveolar wall is mechanically reinforced by a network of elastic and collagen fibers: the elastic fibers facilitate the passive retraction of the lungs during exhalation, while type I and type III collagen fibers prevent the alveoli from overstretching or rupturing. The loss of elastin—for instance, due to proteolytic degradation associated with α_1 -antitrypsin deficiency or smoking—leads to emphysema.

2. Cellular composition of the acinus

Morphometric studies (Crapo et al., 1982) have shown that the alveolar parenchyma of a normal human lung consists of approximately: ~30% endothelial cells, ~36% interstitial cells, ~8% type I alveolar epithelial cells (alveolocytes), ~16% type II alveolar epithelial cells (alveolocytes), and ~10% alveolar macrophages [9]. Approximately 95% of the alveolar surface is covered by type I alveolar epithelial cells, and 5% by type II alveolar epithelial cells..

Cell type	Location	Main functions	Markers
Type I alveolocyte (AT1)	~95% of the alveolar surface	Gas diffusion, barrier	AQP5, PDPN (T1 α), RAGE, HOPX
Type II alveolocyte (AT2)	In the corners of the alveoli, ~5% of the surface area	Surfactant synthesis, stem cell	SFTPC, SFTPB, ABCA3, LAMP3
Alveolar macrophage	In the alveolar space	Phagocytosis, immune surveillance, surfactant clearance	CD68, CD206, MARCO, PPAR γ
Capillary endothelium (gCap, aCap)	Alveolar capillaries	Gas exchange, angiocrine signals	CD31, CAR4, EDNRB
Fibroblast/pericyte	Interstitial	Matrix synthesis, regenerative niche	PDGFR α , LGR5



Cell type	Location	Main functions	Markers
Club (Clara) cell	Terminal/respiratory bronchioles	Secretory, detoxification, progenitor	SCGB1A1 (CC10)

2.1. Type I alveolar cells (pneumocytes I)

These are very flat cells (with a cytoplasmic thickness of 0.05–0.2 μm and a diameter of up to 50–100 μm) that possess long cytoplasmic extensions. A single AT1 cell can cover the surface of several alveoli. They contain few organelles but are rich in pinocytotic vesicles; they are interconnected by tight junctions and adherens junctions, which prevent fluid from leaking into the alveolar space. AT1 cells are incapable of division (they are terminally differentiated); if damaged, they are replaced by type II alveolar cells. They also participate in the transport of water (via aquaporin-5) and ions (via Na^+/K^+ -ATPase and ENaC).

2.2. Type II alveolar cells (pneumocytes II, "cuboidal" cells, or surfactant cells)

AT2 cells are cuboidal or round in shape, located in the corners of the alveoli (at the junctions of the septa), and account for approximately 15% of the cells in the pulmonary parenchyma. Their cytoplasm appears pale (vacuolated), and under an electron microscope, they are characterized by the presence of lamellar bodies—secretory organelles 1–2 μm in diameter that consist of concentric, plate-like, myelin-like structures. There are short microvilli at the tip of the cell. Functions:

- synthesis, storage, exocytosis, and reuptake of surfactant;
- ion and water transport in alveolar fluid (ENaC, Na^+/K^+ -ATPase);
- facultative stem cell function — self-renewal upon injury and differentiation into AT1 cells [4, 5];
- involvement in innate immunity: SP-A, SP-D (collectins), defensins, cytokines (IL-8, GM-CSF), and MHC II expression.

2.3. Alveolar Macrophages

Macrophages located within the alveolar space and on the epithelial surface ("dust cells") originate from two primary sources: resident alveolar macrophages of embryonic origin (yolk sac/fetal liver), which undergo slow self-renewal regulated by GM-CSF/PPAR γ signaling; and interstitial/recruited macrophages derived from blood monocytes. Their functions include the phagocytosis of inhaled particles and microorganisms, the degradation of excess surfactant, and the initiation and subsequent resolution of inflammation. A deficiency in GM-CSF leads to alveolar proteinosis (the accumulation of surfactant). In smokers, these macrophages are often laden with pigments (such as hemosiderin or carbon).

2.4. Capillary Endothelium and Interstitial Cells

Alveolar capillaries form a nearly continuous "sheet-like" network within the pulmonary capillary bed, covering 85–90% of the alveolar wall surface. Modern single-cell analyses have identified at least two major endothelial subtypes: highly specialized "aerocytes" (aCap), which play a primary role in gas exchange, and "gCap" cells, which possess regenerative potential and exhibit stem/progenitor-like characteristics [10]. It has been demonstrated that the endothelium regulates alveolar epithelial proliferation during regeneration via angiocrine signals (MMP14, EGF, HGF).

The interstitium contains fibroblasts, myofibroblasts, pericytes, mast cells, and lymphoid elements. Alveolar fibroblasts (PDGFR α ⁺, some of which are LGR5⁺) serve as a "niche" for AT2 cells, delivering Wnt, FGF, BMP, and IL-1 signals, thereby controlling their self-renewal and differentiation.

2.5. Epithelium of Terminal and Respiratory Bronchioles

The simple cuboidal epithelium of the terminal bronchioles contains ciliated cells (involved in mucociliary clearance) and Club (Clara) cells. Club cells secrete the protein SCGB1A1 (CC10)—which possesses anti-inflammatory and immunomodulatory properties—detoxify toxins via the cytochrome P450 system, and serve as progenitors that can differentiate into bronchial epithelial cells following injury. In the bronchioalveolar junctional region, bronchioalveolar stem cells (BASCs) (SFTPC⁺/SCGB1A1⁺) have been identified (primarily in mouse models) [13]. Neuroendocrine cells within the bronchiolar epithelium—known as neuroepithelial bodies (NEBs)—function as sensors for hypoxia.

3. Histophysiology of the Acinus

3.1. Gas Exchange and Diffusion

The exchange of O₂ and CO₂ occurs via passive diffusion across the air-blood barrier. According to Fick's law, the rate of gas flow is directly proportional to the diffusion surface area and the partial pressure gradient, and inversely proportional to the thickness of the barrier:

$$\dot{V}_{\text{gas}} \propto (A \times D \times \Delta P) / T$$

where A is the diffusion surface area (~130 m²), T is the thickness of the barrier (~0.2–0.6 μ m), D is the diffusion coefficient of the gas, and ΔP is the partial pressure gradient between the alveoli and the capillary blood. The solubility of CO₂ in water is approximately 20–25 times higher than that of O₂; therefore, CO₂ diffusion is not a limiting factor. In contrast, hypoxemia is frequently the initial sign of impaired diffusion.

At rest, an erythrocyte travels through an alveolar capillary in approximately 0.75 seconds. In a healthy individual, O₂ equilibrium is reached within the first ~1/3 of the capillary length (~0.25 s); consequently, a reserve for gas exchange is maintained even during physical exertion (when transit time is reduced to 0.25–0.3 s).



When the alveolar-capillary membrane thickens (due to fibrosis, edema, or inflammation), this reserve is lost, and desaturation occurs during exertion.

3.2. Ventilation-perfusion relationship

The efficiency of gas exchange depends not only on the structure of the acinus but also on the relationship between ventilation ($\dot{V}$) and perfusion ($\dot{Q}$). The $\dot{V}/\dot{Q}$ ratio is high at the lung apices (~ 3) and low at the bases (~ 0.6), with an overall average of approximately 0.8–1. Hypoxic pulmonary vasoconstriction (the Euler-Liljestrand reflex) redirects blood away from poorly ventilated acini toward other regions.

3.3. Surfactant: synthesis, composition, and function

Surfactant is a lipoprotein complex that coats the inner surface of the alveoli, reducing surface tension. It consists of approximately 90% lipids and 10% proteins. The primary lipid component is phosphatidylcholine, of which about 60% is saturated dipalmitoylphosphatidylcholine (DPPC)—the key component responsible for reducing surface tension to near zero. The proteins include hydrophilic SP-A and SP-D (collectins, involved in innate immunity) and hydrophobic SP-B and SP-C (which facilitate the spreading of lipids into a film and stabilize it) [14].

Stages of synthesis:

1. Synthesis of lipids and proteins in the endoplasmic reticulum and Golgi apparatus (the ABCA3 transporter incorporates lipids into lamellar bodies);
2. Accumulation within lamellar bodies ($\text{pH} \approx 5$);
3. Exocytosis (stimulated by respiratory expansion, purines, and catecholamines);
4. Formation of tubular myelin within the alveolus and the creation of a monolayer on the surface;
5. Approximately 70–80% of the used surfactant is reabsorbed (reuptake) by AT2 cells, while the remainder is degraded by macrophages..

The physiological significance of surfactant is explained by the Laplace equation: $P = 2T / r$. In the absence of surfactant, pressure in small alveoli would be high, causing them to collapse, with air "flowing" into larger alveoli. By significantly reducing surface tension—especially in structures with a small radius—surfactant stabilizes the alveoli, reduces the work of breathing, and helps keep the alveoli dry. In premature infants (up to 28–34 weeks of gestation), the immaturity of type II alveolar epithelial cells (AT2 cells) is the cause of respiratory distress syndrome; meanwhile, mutations in the *SFTPB*, *SFTPC*, and *ABCA3* genes lead to hereditary surfactant dysfunction and childhood interstitial lung diseases.

3.4. Alveolar Fluid Balance

The fluid layer on the surface of the alveoli must be extremely thin ($\sim 0.2 \mu\text{m}$). Hydrostatic pressure within the blood capillaries and the protein-oncotic gradient drive the filtration of fluid into the interstitium, while excess fluid is removed via lymphatic vessels. The primary mechanism for clearing fluid that has entered the alveoli involves Na^+ transport by AT1 and AT2 cells—specifically, the entry of Na^+



through apical ENaC channels, its exit via basolateral Na⁺/K⁺-ATPase, and the osmotic movement of water through aquaporins [15]. This mechanism plays a crucial role in the resolution of pulmonary edema and the absorption of fetal fluid during the first breath after birth. Damage to the alveolar epithelium (due to viral pneumonia, ARDS, or reperfusion) disrupts this transport, leading to prolonged alveolar edema.

3.5. Defense Mechanisms

Defense within the acinus operates at several levels:

- mucociliary clearance — present up to the level of the respiratory bronchioles (via ciliated epithelium and a mucus layer), though it is virtually absent within the acinus itself;
- alveolar macrophages — the primary "cleansing" cells, which remove phagocytosed particles via the mucociliary escalator and lymphatic vessels;
- surfactant proteins (SP-A, SP-D) — these opsonize bacteria, viruses, and fungi, promote agglutination, and enhance phagocytosis by macrophages;
- epithelial barrier — comprising tight junctions, antimicrobial peptides (defensins, lysozyme, lactoferrin), and secretory IgA;
- bronchus-associated lymphoid tissue (BALT) and interstitial dendritic cells — the starting point for adaptive immunity.

Together, these elements continuously protect the lung tissue from the impact of the external environment; however, excessive inflammation can also lead to severe damage to the alveolar walls.

4. Lung Regeneration

4.1. Development and Alveolarization: The Foundation for Regeneration

During embryonic development, the lung forms from the endoderm and progresses through four stages: pseudoglandular, canalicular, saccular, and alveolar. The majority of alveoli are formed after birth (alveolarization: the development of secondary septa and the maturation of the capillary network). It was previously believed that alveolarization concluded around the age of 2–3 years; however, recent studies have shown that the number of alveoli continues to increase as a child grows, extending into adolescence. Since regeneration largely involves the reactivation of developmental programs, signaling pathways such as FGF10/FGFR2b, Wnt, Notch, Hippo/YAP-TAZ, BMP, and TGF-β play a central role in both processes [3, 6].

4.2. Homeostatic (Physiological) Renewal

In a healthy lung, cell turnover occurs slowly. In mice, the average lifespan of AT2 cells has been estimated to be approximately 4–40 weeks (varying depending on the research methodology); In the human lung, this duration has not been precisely measured, but it is estimated to be on the order of months to years. Under homeostatic conditions, a small, frequently dividing subpopulation of AT2 cells (the Axin2⁺/Wnt-responsive population) renews the alveolar surface, while bronchial basal cells (KRT5⁺/TP63⁺) renew the epithelium of the proximal airways.

4.3. Post-injury regeneration: AT2 cells as central stem cells

Injury to the alveolar epithelium (caused by influenza virus, bleomycin, hyperoxia, ARDS, smoking, or reperfusion) leads to the loss of AT1 cells. Lineage tracing experiments (Barkauskas et al., 2013) have demonstrated that AT2 cells function as facultative stem cells, capable of self-renewal and differentiation into AT1 cells [4]. Furthermore, HTII-280⁺ AT2 cells isolated from human lungs have exhibited this same capacity in organoid cultures.

Regeneration consists of the following stages:

1. Injury and inflammation phase: death of AT1 cells, exposure of the basement membrane, infiltration by neutrophils and monocytes, and the release of IL-1 β , TNF, and IL-6.
2. Proliferation phase: AT2 cells become activated (driven by FGF7/FGF10, EGF, HGF, Wnt, and YAP/TAZ signaling) and proliferate; fibroblasts and endothelial cells in the interstitium also undergo proliferation.
3. Transient differentiation state: a recently described intermediate cell state—known in mice as Krt8⁺/Cldn4⁺/Sfn⁺, DATP, or PATS, and associated with "aberrant basaloid" and KRT5⁻/KRT17⁺ cells in humans—emerges during the transition from AT2 to AT1 cells. Under normal resolution, these cells rapidly differentiate into AT1 cells; their persistence is considered a key mechanism in the development of fibrosis [19–21].
4. Resolution phase: new AT1 cells are generated, restoring the barrier; excess cells are eliminated via apoptosis; the matrix undergoes remodeling; and inflammation subsides..

AT2 cells are not homogeneous: in both mice and humans, a Wnt-responsive AXIN2⁺/TM4SF1⁺ subpopulation is characterized by stem cell activity; this subpopulation is located in close proximity to fibroblasts within the AT2 niche [16, 22]. In the human lung, recent single-cell atlas studies (Travaglini et al., 2020) have revealed an extensive list of cell types and identified novel populations (e.g., terminal respiratory bronchiole secretory cells, TRB-SCs).

4.4. Other progenitors of the distal airway

In cases of severe injury (such as H1N1 influenza pneumonia), when AT2 cells are insufficient, other progenitors are recruited:

- Basal-like distal airway stem cells (KRT5⁺/TP63⁺, "pods"): In mice, following influenza-induced injury, these cells migrate from the bronchioles into the alveoli to form "KRT5-pods." While they undergo partial differentiation into alveolar cells, the extent to which they can fully restore functional AT2/AT1 cells remains a subject of debate [25, 26];
- Bronchoalveolar stem cells (BASCs): SFTPC⁺/SCGB1A1⁺, located at the bronchioalveolar junction; these have demonstrated bipotent activity **in vitro** in mice, though their prevalence **in vivo** varies depending on the analytical method used [13];



- Club cells: In the bronchioles, Club cells regenerate ciliated and other cell types; under certain conditions—such as severe injury or the loss of basal cells—they may also transdifferentiate into AT2 cells;
- Endothelium: Capillary endothelial cells proliferate following injury to drive angiogenesis and influence epithelial regeneration through the secretion of angiocrine factors [11].

4.5. The Regenerative Niche

A cell's stem-like properties are determined by its microenvironment (niche). The AT2 niche includes the following:

- Fibroblasts — which produce Wnt (WNT2, WNT5A), FGF7/FGF10, IL-1 β , and BMP signaling molecules;
- Endothelium and pericytes — angiocrine factors, composition of the basement membrane;
- Macrophages — IL-1 β , IL-6, TGF- β ; determine the inflammatory tone;
- Extracellular matrix (ECM) — stiffness, laminin, collagen IV, fibronectin; influences cellular state via YAP/TAZ mechanotransduction.

Thus, regeneration is not merely an "internal" program of the epithelium, but the result of an intercellular signaling network; if this network is disrupted, regeneration culminates in fibrosis or emphysema.

4.6. Compensatory Growth

When a portion of the lung is removed (pneumonectomy, lobectomy), the remaining lung tissue exhibits compensatory growth. The synthesis of new alveoli (neo-alveologenesis) has been demonstrated in mice and dogs; this process is driven by the proliferation of alveolar epithelium and endothelium, mechanical stretch, and hormonal factors (such as retinoic acid). In humans, Butler et al. (2012) documented an increase in pulmonary diffusion capacity and the surface area of the alveolar-capillary membrane in a young patient following a pneumonectomy, indicating that a certain capacity for growth exists in humans as well [27]. However, compensatory growth is not equivalent to complete regeneration: in humans, the increase in the number of new alveoli is limited and age-dependent.

4.7. Impaired Regeneration: Fibrosis and Emphysema

In idiopathic pulmonary fibrosis (IPF), recurrent micro-injuries and the dysfunction of AT2 cells (involving telomere shortening, ER stress, and mutations in *SFTPC*, *TERT*, or *TERC*) impair the repair process; "Aberrant" interstitial cells accumulate, fibroblasts/myofibroblasts become activated, and collagen deposition occurs, leading to a disruption of tissue architecture (the "honeycomb" appearance). The hallmark histological feature is the "UIP" (usual interstitial



pneumonia) pattern, characterized by a basal and subpleural distribution, fibroblastic foci, and dense collagen [20, 21].

In emphysema—a component of chronic obstructive pulmonary disease (COPD)—a protease-antiprotease imbalance, oxidative stress, and the apoptosis of alveolar cells lead to the loss of alveolar walls; this results in the dilation of acinar spaces and a reduction in the respiratory surface area. Depending on which part of the acinus is affected, emphysema is classified into centriacinar (proximal; typically seen in smokers), panacinar (involving the entire acinus; associated with α 1-antitrypsin deficiency), and paraseptal types. These classifications are clinically significant due to their relationship with the structure of the acinus.

Currently, there is no established therapy capable of fully restoring alveoli lost to emphysema. While retinoids, mesenchymal stromal cells, and FGF/Wnt modulators are being investigated in experimental and clinical trials, the results have been limited.

5. Lung Transplantation

5.1. Historical Background

The first human lung transplantation was performed by J. Hardy in 1963, but the patient died 18 days later; during the 1960s and 1970s, long-term success was not achieved due to issues with bronchial anastomosis healing and organ rejection [28]. Following the clinical introduction of cyclosporine and improvements in bronchial anastomosis techniques, the Toronto group reported a patient (with pulmonary fibrosis) who survived long-term after a single-lung transplant in 1983 (published in the NEJM in 1986) [29]. Subsequently, bilateral sequential transplantation, heart-lung transplantation, and lobar transplantation from a living donor were developed.

5.2. Indications and Types of Transplantation

The most common indications include: chronic obstructive pulmonary disease (emphysema), idiopathic pulmonary fibrosis, cystic fibrosis, pulmonary arterial hypertension, α 1-antitrypsin deficiency, sarcoidosis, and lymphangioleiomyomatosis. In recent years, idiopathic pulmonary fibrosis (IPF) and irreversible ARDS associated with COVID-19 have also become indications for transplantation.

Types:

- Single lung — primarily for older patients (e.g., with IPF or emphysema); effective when there is a shortage of donor lungs.
- Bilateral (double lung) — currently the most common approach; mandatory in cases of cystic fibrosis and bronchiectasis (to ensure no source of infection remains), and some data suggest better long-term outcomes.
- Heart-lung complex — indicated for Eisenmenger syndrome and combined heart-lung pathology.



- Lobar transplantation from a living donor — typically involves lower lobes from two separate donors (used for children and smaller-framed adults); its use is limited due to the risks posed to the donors.

In the United States, the Lung Allocation Score (LAS) was used for donor selection starting in 2005, and it was replaced by the Composite Allocation Score (CAS) in March 2023; similar systems also exist in Europe.

5.3. Donor Lungs and Preservation

Donor lungs are procured from donors following brain death (DBD) or circulatory death (DCD). Only a small proportion (approximately 15–20%) of donor lungs are suitable for transplantation, as complications such as neurogenic edema, aspiration, infection, barotrauma, and ventilator-induced injury are common. Regarding preservation—specifically cold static storage (at 4–10 °C using an extracellular, low-potassium, dextran-containing solution, such as Perfadex)—the recommended duration of total tissue ischemia is up to approximately 6–8 hours.

Ex vivo lung perfusion (EVLP) is a method for assessing and restoring organ function by perfusing and ventilating the organ outside the body under normothermic conditions. The Toronto group (Cypel et al., 2011) demonstrated that a certain proportion of lungs—initially deemed unsuitable—could be rendered viable for transplantation through EVLP, with outcomes comparable to those achieved using standard methods [30]. Furthermore, the possibility of administering pharmacological or gene therapy (for example, an IL-10 gene vector) to the organ during EVLP is being explored.

5.4. Transplant Histopathology

a) Ischemia-reperfusion injury and primary graft dysfunction (PGD). Develops within the first 72 hours post-transplantation; according to the ISHLT definition, it is classified into grades 0–3 based on the PaO₂/FiO₂ ratio and radiographic infiltrates [31]. Histologically: presents as diffuse alveolar damage (DAD) — alveolar edema, hyaline membranes, neutrophilic infiltration, necrosis of type I alveolar epithelial cells (AT1), and hyperplasia of type II alveolar epithelial cells (AT2). Mechanisms: reactive oxygen species, complement activation, activation of donor macrophages and endothelium, and an "innate" immune response.

b) Acute cellular rejection (ACR). Histological classification is assessed via transbronchial biopsy according to the ISHLT 1996 criteria (updated in 2007 by Stewart et al.):

- Grade A (perivascular): A0 — none; A1 — minimal (sparse perivascular mononuclear infiltrate); A2 — mild; A3 — moderate; A4 — severe (infiltrate extending into the alveoli, pneumocyte damage, hyaline membranes).

- Grade B (lymphocytic bronchiolitis/airway inflammation): B0 — none; B1R — minimal to mild; B2R — high-grade; BX — ungradable. The perivascular infiltrate is primarily associated with CD4⁺ and CD8⁺ T-lymphocytes directed against

donor antigens (HLA), initiated via both direct and indirect allorecognition pathways. Acute rejection typically responds well to steroid pulse therapy; however, recurrent episodes increase the risk of chronic rejection.

C) Antibody-mediated rejection (AMR). This is characterized by the presence of antibodies against donor-specific antigens (DSA), deposition of the complement fragment C4d on the capillary endothelium, capillaritis, and the accumulation of neutrophils; the diagnosis of pulmonary AMR is based on a combination of clinical, serological (DSA), and histological criteria.

d) Chronic lung allograft dysfunction (CLAD). This is the most serious complication determining long-term post-transplant outcomes, developing in approximately 50% of patients within 5 years. Two main phenotypes are distinguished:

- Bronchiolitis obliterans syndrome (BOS) — an obstructive type; its histological basis is obliterative bronchiolitis, characterized by lymphocytic inflammation in the small airways (membranous and respiratory bronchioles), loss of epithelium, formation of granulation tissue, and subsequent obliteration of the airway lumen by dense fibrosis.

- Restrictive allograft syndrome (RAS) — a restrictive type; characterized by fibrosis in the pleura and interstitium, alveolar fibroelastosis, and "alveolar-interstitial" inflammation; it carries a poorer prognosis.

In addition to alloimmunity, the pathogenesis of CLAD involves factors such as diffuse alveolar damage (DAD), primary graft dysfunction (PGD), recurrent infections (CMV, *Pseudomonas*, *Aspergillus*), gastroesophageal reflux and aspiration, donor-specific antibodies (DSA), epithelial-mesenchymal transition, and the loss of epithelial progenitor cells in the bronchioles. Thus, CLAD is the combined result of the exhaustion of the acinus's regenerative capacity and immune-mediated injury.

5.5. Immunosuppressive Therapy and Infections

The standard regimen consists of three components: a calcineurin inhibitor (tacrolimus), an antiproliferative agent (mycophenolate mofetil), and corticosteroids (prednisolone). For induction, antibodies against the IL-2 receptor (basiliximab) or antithymocyte globulin are used. In lung transplantation, a more potent immunosuppressive regimen is required compared to other organ transplants, as the lungs are in constant contact with the external environment and contain a large amount of lymphoid tissue. Potential complications include infectious complications (CMV, bacterial infections, *Aspergillus*), renal failure, diabetes mellitus, and malignancy (skin cancer, post-transplant lymphoproliferative disorder).

5.6. Outcomes

According to data from the International Society for Heart and Lung Transplantation (ISHLT) registry, the median survival time following lung transplantation is approximately 6–7 years; 1-year survival is approximately 85–90%, and 5-year



survival is approximately 55–60%. These figures are lower than those observed for heart or kidney transplantation [35]. Outcomes are better in younger patients and in centers with greater experience.

6. Promising Directions

6.1. Decellularization and Bioengineered Lungs

The essence of the method: cells are washed out of a donor lung (via perfusion with detergents), leaving behind a non-immunogenic extracellular matrix scaffold (composed of collagen, elastin, and laminin), which is subsequently repopulated with the recipient's own cells (recellularization). Ott et al. (2010) and Petersen et al. (2010) utilized this approach to create bioengineered lungs in rats, demonstrating gas exchange over a short period [36, 37]. Key challenges include: achieving complete endothelialization of the vascular network (to prevent blood clotting and extravasation), restoring the alveolar epithelial barrier, ensuring the correct spatial arrangement of diverse cell types, maintaining long-term function, and securing a sufficient source of cells for a full-sized organ. At present, this approach is not yet ready for clinical application.

6.2. iPSCs and Organoids

Methods have been developed to derive functional AT2-like cells and alveolar organoids from induced pluripotent stem cells (iPSCs) [38]. While organoids are valuable for studying regenerative mechanisms, conducting drug screening, and establishing disease models, they cannot fully replicate the structure of an alveolus or acinus, nor can they reproduce the necessary blood supply. Transplantation of AT2 cells for cell therapy is being studied in mouse models.

6.3. Cell and gene therapy

Mesenchymal stromal cells (MSCs) possess immunomodulatory and regenerative effects, yet their efficacy in clinical trials has been limited. Delivering gene therapy (e.g., IL-10, anti-apoptotic genes, SERPINA1, etc.) to an "isolated" organ during EVLP (ex vivo lung perfusion) is a promising approach. In cystic fibrosis, the use of CFTR modulators (elexacaftor/tezacaftor/ivacaftor) has significantly reduced the need for transplantation.

6.4. Xenotransplantation

Genetically engineered porcine organs—from which antigens responsible for hyperacute rejection have been removed and into which human complement-regulatory genes have been introduced—have been used in initial clinical trials involving kidneys and hearts. Xenotransplantation of the lungs is one of the most complex areas, as the lungs are in contact with the external environment and are highly immunogenic; nevertheless, preliminary data have been reported regarding the short-term function of a porcine lung in a human recipient who had been declared brain-dead. However, this field remains in the experimental stage.

6.5. Future Directions



A profound understanding of acinar histophysiology and the mechanisms of regeneration provides the foundation for developing: (1) pharmacological agents that activate alveolar progenitors; (2) therapies that halt or reverse fibrosis; (3) technologies to restore donor lungs for transplantation; and (4) strategies to prevent CLAD (chronic lung allograft dysfunction).

Conclusion

1. The acinus is the gas-exchange unit of the lung, supplied by a terminal bronchiole and consisting of respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli. Its efficiency is determined by the thinness of the air-blood barrier (0.2–0.6 μm), a large respiratory surface area ($\sim 130 \text{ m}^2$), the presence of surfactant, and an adequate blood supply.

2. Type I alveolar epithelial cells (alveolocytes) facilitate gas diffusion, while Type II alveolar epithelial cells are responsible for surfactant synthesis and regeneration; together with macrophages, endothelial cells, and fibroblasts, they form a unified functional system.

3. Regeneration is primarily driven by AT2 cells (facultative stem cells) and distal airway progenitors, regulated by niche signals (Wnt, FGF, YAP/TAZ, IL-1 β) and the extracellular matrix (ECM). Impairment of this regenerative process leads to fibrosis and emphysema.

4. Lung transplantation serves as the only definitive treatment for end-stage lung diseases; however, outcomes are limited by primary graft dysfunction (PGD), acute or antibody-mediated rejection, and, in particular, chronic lung allograft dysfunction (CLAD)—encompassing both bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). The shortage of donor organs is being partially mitigated through technologies such as ex vivo lung perfusion (EVLP).

5. In the future, decellularization/recellularization, iPSC-organoids, cell and gene therapy, and xenotransplantation will open up new possibilities for regenerative medicine; however, extensive further research is required before they can be applied clinically.

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