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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Review Article

History and Mystery of Pulmonary Surfactant Membranes

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Received: August 15, 2023; **Published:** September 04, 2023

Abstract

The lung is a complicated organ. Lungs play a pivotal walk on part in safeguarding cellular respiration. The lung epithelium is concealed by pulmonary surfactant, which is an intricate membranous proteolipid film that keeps going lung function.

Epithelial alveolar type 2 cells secrete alveolar epithelium. Pulmonary surfactant is the first respiratory barrier against inhaled foreign matter and microorganisms. This pulmonary surfactant lessens surface tension.

Pulmonary surfactant deficiency is associated with respiratory pathologies, and treatment often includes supplementation with exogenous materials.

The respiratory membrane contains type 1, and type 11 Alveolar epithelial cells, endothelial and fibroblasts. Pulmonary surfactant (PS) is a lipid-protein complex essential to stabilize the alveoli.

Keywords: *Type 1 and Type 11 Alveolar Epithelial Cells; Endothelial; Fibroblasts; Extracorporeal Membrane Oxygenation*

Introduction

The alveolar epithelium is involved in lung immune response [1].

Alveolar epithelium is in proximity with the endothelial monolayer of the pulmonary capillary network [2].

The exhaled breath CO (eCO) is considered a potential biomarker for oxidative stress and respiratory diseases [3].

The lung alveolus is disturbed by acute lung injury and viral infection [4,5].

The protein transport, translocation, regulate fluid fluxes and ion transport [6,7].

AT2 cells are cuboidal secretory cells that are essential for the maintenance of alveolar epithelial homeostasis [8].

Alveolar Epithelial cell11 (AEII) cells are vulnerable to mechanical stress [9].

Alveolar epithelial type II (AEII) cells targets in many lung diseases, including acute respiratory distress syndrome, and pulmonary fibrosis [10].

Endothelial cells (ECs) lining the blood vessels are important players in many biological phenomena but are crucial in hypoxia-dependent diseases where their deregulation contributes to pathology [11].

The endothelium maintains homeostasis, blood pressure, blood coagulation, and fibrinolysis [12].

Extra Corporeal Membrane Oxygenation (ECMO) has become an essential tool in the care of adults and children with severe cardiac and pulmonary dysfunction refractory to conventional management [13].

Analogous to phospholipids, some polymers assemble into vesicles and can mimic cellular membranes [14].

This incentive holds also in the case of cell membranes, where the scaffold phospholipids can be replaced with other amphiphilic molecules like synthetic polymers or blended with them in hybrid systems into the form of chemical prosthetics [15].

Polymer vesicles (polymersomes) have a similar structure to liposomes and result from the self-assembly of polymers into monolayers (graft and triblock copolymers) or bilayers [16].

(PDMS) Polydimethylsiloxane is the most studied and representative membrane for ventilation and nutrient exchange [17].

PDMS is transparent, oxygen-permeable, stretchable, and flexible allowing the precise imitation of the alveolar dynamic mechanical deformation caused by breathing [18].

Other polymer films have also been widely applied and are easy to manufacture, flexible, and cost-effective [19].

Air-liquid exchange membranes have also been built using polyester (PET) and polymethyl methacrylate (PMMA) [20].

History

The presence of a pulmonary surfactant was directly linked with respiratory failure by Richard Pattie in England and John Clemens in the USA while studying the effects of nerve gases in the lungs [21].

Adams and Fujiwara in the USA showed the same beneficial effects of natural surfactants in preterm lambs [22].

Pulmonary cells

The arrangement of alveolar cells is a basic functional unit in the lung-on-a-chip [23].

The respiratory epithelium is the ciliated pseudostratified columnar epithelium [24].

The pulmonary epithelium consists of two major cell types-alveolar type I (ATI) cells and alveolar type II (ATII) cells, also termed type I and type II pneumocytes [25].

Alveolar epithelial type I cells

ATI cells are highly specialized for the key function of the lungs-the gas exchange between alveoli and capillary blood.

Facilitate gas exchange, maintain ion and fluid balance within the alveoli, and Communicate with type II pneumocytes to secrete surfactant in response to stretch. ATI cells can play an important role in the pathogenesis of lung damage.

Alveolar epithelial type II cells

Produce and secrete pulmonary surfactant.

ATII cells play a crucial role in lung repair/regeneration after injury [26].

Alveolar type II cells (ATIIs) synthesize and secrete pulmonary surfactant, secrete chemokine and cytokines, and participate in the innate immune response of the lung.

ATII cells are responsible for repairing damaged tissue. Furthermore, the depletion of this cell population may lead to various pulmonary diseases [27].

ATII cells maintain a sufficient respiratory surface area of the mammalian lungs at the end of expiration [28].

Surfactant proteins (SPs) SP-A and SP-D, which act as opsonins and regulate the function of inflammatory cells, are best characterized. ATII cells represent endogenous antimicrobial peptides (neutrophil α-defensins, β-defensins, cathelicidin hCAP18/LL-37) in the lungs.

Pulmonary hypoxia is a consequence of chronic obstructive pulmonary disease (COPD), lung tumors, pulmonary hypertension, edema, and others.

During embryonic development, the lungs are the last organs to develop. At week 35 of gestation, the lungs are ready to breathe, and alveolar epithelial type II (ATII) cells have already synthesized surfactant [29].

The basal membrane of these cells is in close contact with endothelial cells from the capillary; therefore, through the ATI cell, gas exchange occurs from alveolar spaces to the lumen of capillaries [30].

Alveolar macrophages

Macrophages are large eaters. Macrophages are involved in the processing of antigens before they are presented to the T and B cells.

Functions of alveolar macrophages

Macrophages are innate immune cells present in every tissue and necessary for homeostasis. Macrophages sense and respond to pathogens and other environmental challenges and participate in tissue repair after injury. Macrophages are large eaters. These cells clear the dust particles, microorganisms, and other debris [31].

Bio artificial membranes

Membrane technology is playing a crucial role in cutting-edge innovations in the biomedical field. Surface engineering is widely used while developing membranes for its use in bioartificial organ development, separation processes, extracorporeal devices, etc [32].

Membranes are a crucial part of man-made or natural macro-microsystems, used in separation processes, directly or indirectly affecting human life [33].

Extracorporeal membrane devices (ECMDs), the membranes act as a barrier between two fluidic systems; drug delivery vehicles where membranes act as a reservoir for controlled and sustained delivery of drugs, etc [34].

Researchers make the proton pump of the respiratory chain work in an artificial polymer membrane

In a recent study, the researchers looked for an artificial polymer that has the properties of a cell membrane and could also play its role in energy metabolism. Natural cell membranes, which consist of phospholipids, separate the cell interior from the environment.

Proton pump in an artificial membrane

The researchers have now found a commercially available polymer (the surfactant PDMS-*g*-PEO) that acts as a membrane in place of the natural phospholipids and can thus form vesicles [35].

Polymeric membranes

Polymeric membranes are made of cellulose acetate (CA), polysulfone (PSF), polydimethylsiloxane (PDMS), polycarbonate (PC) and polyimide (PI) [36,37].

PDMS (polydimethylsiloxane) due to its higher gas permeability in comparison with other synthetic polymers was viewed as a remarkable candidate When compared to rubbery membranes, glassy membranes have high glass transition temperature (Tg) and glassy membranes also have high selectivity CO_2/CH_4 [38].

Disadvantages

(1) While handling Carbon dioxide, they might experience plasticization problems.

(2) Swelling of the polymer increases when the membrane is exposed to CO_2 which in turn results in an increase in permeability of all the components of gas [39].

Inorganic membranes offer more thermal stability, are resistant to chemicals, and also offer better mechanical strength, so they are considered more advantageous than Conventional polymeric membranes. They are normally made using zeolites, carbon molecular sieves (CMS), metal-organic frameworks, and ceramics [40].

Inorganic membrane fabrication is a tough process and there is a need for continuous monitoring because of their delicate structure [41].

Different methods are used to fabricate the membranes, are interfacial polymerization, phase inversion, track etching, controlled stretching, melt extrusion, and electro-spinning [42].

Separation through a membrane usually takes place according to membrane morphology and the mechanisms of transport including Knudsen diffusion, solution diffusion, and molecular sieving [43].

Principles of CO2 diffusion and transport

Carbon dioxide is an important side product of both glycolysis and the citric acid cycle (Krebs cycle) [44].

Mechanism of transport of CO2

Oxygen combines with glucose to form carbon dioxide, adenosine triphosphate, and water at the cellular level.

There are three means by which carbon dioxide is transported in the bloodstream from peripheral tissues and back to the lungs: (1) dissolved gas, (2) bicarbonate, and (3) carbaminohemoglobin bound to hemoglobin (and other proteins) [45].

Chloride shift

Bicarbonate (HCO_3^-) is the transport form of carbon dioxide which contributes about 70% of the total carbon dioxide (CO_2) content of the body. CO_2 reacts with H_2O and gets converted to carbonic acid (H_2CO_3), the reaction is mediated by the carbonic anhydrase present abundantly in RBC. Further carbonic acid partially dissociation into hydrogen ions (H^+) and bicarbonate ions (HCO_3^-) as it is a weak acid. The so-formed bicarbonate ion gets diffused out of RBC in plasma and gets combined with Sodium (Na^+) ion and gets converted to sodium bicarbonate ($NaHCO_3$). A positive charge gets attained in RBC due to the loss of bicarbonate which is balanced by the entry of Chloride (Cl^-) into RBC from plasma. This exchange of ions is termed as chloride shift. This phenomenon is otherwise known as the Hamburger phenomenon.

Pathophysiology

In the bloodstream, dissolved CO_2 is neutralized by the bicarbonate-carbon dioxide buffer system where it forms a weak acid, carbonic acid (H_2CO_3). H_2CO_3 can dissociate into a hydrogen ion and a bicarbonate ion [46,47].

$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$.

When CO_2 levels are high, there is a right shift in the reaction mentioned above. As a result, the concentration of H^+ ions in the bloodstream rises, lowering the pH and introducing a state of acidosis. In contrast, when CO_2 levels are low, there is a left shift in the reaction, resulting in an alkalotic state.

Carbonic anhydrase catalyzes the conversion of CO_2 and water to H^+ and bicarbonate.

$CO_2 + H_2O \rightarrow H^+ + HCO_3^-$.

Carbonic anhydrase helps to maintain the acid-base balance in the bloodstream and is present in high concentrations in erythrocytes.

Clinical significance

Clinically, transportation and elimination of carbon dioxide become especially crucial in regulating the pH of the blood. Should the partial pressure of carbon dioxide increase or decrease, the body's pH will decrease or increase, respectively. This change can occur as a primary disorder, such as in the case of an individual who becomes apneic and develops acidosis because of the increased partial pressure of carbon dioxide, or as a compensatory reaction, such as in a person with diabetes who develops ketoacidosis and hyperventilates to decrease carbon dioxide levels and prevent the pH from dropping too low.

Pulmonary drug delivery

Lungs are an important target for drug delivery at pulmonary and systemic circulation sites. The bioavailability of drugs are much

more inspite of the presence of metabolizing enzymes of Cytochrome P450 (CYP 450). Drugs delivered through this route bypass the acid and other factors involved in drug absorption from the gut. The drug particle size should be taken into consideration and should be < 1 μm for efficient pulmonary delivery. The overall factors to be considered are particle density, hygroscopicity and electrical charge. Surfactant - drug interactions can sometimes increase the solubility of the drug, thus favoring absorption and bioavailability. The devices existing for drug delivery are important like metered dose inhaler (MDI), dry powder inhaler (DPI)/rotahalers and nebulisers are devised for the same. Extracorporeal membrane oxygenation (ECMO) is an emergency life support procedure. Novel drug delivery is not only important for better bioavailability but also for reduced adverse drug effects. This mode of drug delivery is looked upon as a futuristic model too. Nanoparticles like liposomes, lipid nanoparticles, polymeric nanoparticles, polymeric micelles are the drug delivery models in future. The term 'nano' refers to the drug particle size between 1 - 1000 nm. The possibility of pulmonary surfactant (lipid rich) as a drug carrier for lipid soluble drugs is explored with drugs like Tacrolimus and Amikacin to name a few. Pulmonary vaccination can be the way forward for respiratory diseases as well, particularly for pneumonia and influenza. Imaging technique which is aerosol driven can be a futuristic diagnostic procedure. Use of radiolabelled biomarkers like Technetium-99 conjugated epidermal growth factor receptor (EGFR), folate, anaplastic lymphoma kinase (ALK), proto-oncogene B-Raf (BRAF) are studied as diagnostic tools.

Surfactant nebulization

Surfactant replacement therapy (SRT) is a standard treatment modality in neonatal respiratory distress syndrome (RDS). It is known to decrease acute pulmonary morbidity and mortality in preterm infants. For decades, this beneficial replacement therapy has been administered via an endotracheal tube which has its own limitations and complications. This has led to the gradual evolution of noninvasive ventilation strategies in neonatal RDS.

To minimize the risk of ventilation-induced injury, the use of nasal continuous positive airway pressure (nCPAP) has become the favored strategy for early respiratory management of preterm infants. Efficient nCPAP is key to maintaining the functional residual capacity of the immature lung. It promotes endogenous surfactant production, which typically takes place on the second or third day of life.

Nebulization is a truly noninvasive approach of surfactant administration as it avoids any airway manipulation at all. Moreover, data from animal models suggest improved distribution of surfactant with minor systemic and cerebral hemodynamic side effects. Subsequent studies did not show beneficial effects of dipalmitoyl-phosphatidylcholine aerosol in neonatal RDS and discouraged surfactant aerosolization. Later studies in animal and *in vitro* models helped to develop efficient aerosol devices which can establish adequate pulmonary deposition. This has reawakened interest in aerosol surfactant administration along with stepwise implementation of CPAP and noninvasive ventilation in neonatal practice.

Factors determining pulmonary delivery and efficacy

Difficulties in pulmonary deposition and distribution of aerosolized surfactant arise from particle size, dose and stability of formulation during nebulization. Different types of nebulizers have been tested. While jet nebulizers often result in pulmonary deposition of < 1 - 5% of aerosols, evolution of vibrating membrane nebulizers has improved aerosolization with deposition rates of ≥ 20% reported in animal and *in vitro* models with pulmonary responses potentially similar to intra-tracheal surfactant in terms of oxygenation and lung mechanics.

Aerosolization of synthetic surfactant preparations

Few synthetic surfactants have been subjected to nebulization in animal and *in vitro* models. Synthetic formulations are different from natural surfactants with standardized and potentially optimized composition and increased resistance against inactivation.

Extracorporeal membrane oxygenation (ECMO)

In severe and life-threatening conditions, ECMO life support is used. The ECMO machine is similar to the heart-lung bypass machine. It pumps and it rests the heart and lungs, by allowing oxygenates a patient's blood outside the body. Through artificial lung, blood flows in the machine that adds oxygen and takes away carbon dioxide.

Blood flows back into the patient's body, after warming to body temperature.

There are two types of ECMO. The VA ECMO is connected to both a vein and an artery and is used when there are problems with both the heart and lungs. The VV ECMO is connected to one or more veins, usually near the heart, and is used when the problem is only in the lungs.

The perfusionist or ECMO specialist will adjust the settings on the machine to give the most appropriate support to the patient's vital organs.

Uses of ECMO

Procedure

The patient is sedated, given pain medications and anti-coagulants to minimize blood clotting. A surgeon, assisted by an operating room team, inserts the ECMO catheters into either an artery or veins. An x-ray is then taken to ensure the tubes are in the right place.

Cardiac conditions	• Acute massive myocardial infarction • Decompensated cardiomyopathy • Myocarditis • Post cardiac surgery • Post cardiac transplant complications • Cardiogenic shock • As a bridge to a heart assist device
Pulmonary conditions	• Acute respiratory distress syndrome (ARDS) • Pulmonary embolism • Covid 19 and other pneumonia • Congenital diaphragmatic hernia • Meconium aspiration • Pulmonary hypertension • Respiratory failure • As a bridge for patients awaiting lung transplant
Other conditions	• Life-threatening response to infection (sepsis) • Low body temperature (severe hypothermia) • Trauma • Post organ transplant sepsis

Discontinuing ECMO requires a surgical procedure to remove the tubes. Multiple tests are usually done prior to the discontinuation of ECMO therapy to confirm the adequate functioning of the heart and lungs. Off ECMO, the patient may still continue to be on a mechanical ventilator for some time.

Risks

ECMO does carry risks including:

1. Bleeding due to medications that are given to prevent blood from clotting.
2. Infection at the sites where the tubes enter the body.
3. ECMO patient is given blood products and hence possibility of transfusion problems may arise.

Limitations

An ECMO machine can help support a person's life, but it does not treat the disease or injury that led to the heart and lung failure.

Conclusion

The lungs transport oxygen from the atmosphere into the blood circulation and keep the pulmonary tissue free of pathogens. The effect of Lipopolysaccharide (LPS) on the pulmonary alveoli is complex.

This process results in disruption of alveolar epithelial and endothelial barriers. LPS also interferes with the ability of ATII cells to produce pulmonary surfactant and LPS itself binds to surfactant proteins and phospholipids leading to surfactant inactivation. The leak of protein-reach plasma into the airspaces and surfactant inactivation is an initial step of ARDS and thus LPS-induced lung injury may be a serious clinical problem.

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Volume 12 Issue 8 August 2023