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REVIEW

New insights in ARDS pathogenesis

Paloma González-Rodríguez[1], Raquel Herrero[1,2,3,*], Gema Sánchez[1,4], Jose Angel Lorente[1,2,3,5,6]

[1]Foundation for Biomedical Research of the Getafe University Hospital, 28905 Getafe, Madrid, Spain
[2]Department of Critical Care Medicine, Getafe University Hospital, 28905 Getafe, Madrid, Spain
[3]CIBER of respiratory diseases (CIBERES), Carlos III Health Institute, 28029 Madrid, Spain
[4]Department of Clinical Analysis, Getafe University Hospital, 28905 Getafe, Madrid, Spain
[5]Clinical Department, European University of Madrid, 28670 Villaviciosa de Odón, Madrid, Spain
[6]Department of Bioengineering, Carlos III University, 28911 Leganés, Madrid, Spain

***Correspondence**
raquelher@hotmail.com
(Raquel Herrero)

Abstract

Acute respiratory distress syndrome (ARDS) is a life-threatening condition in critically ill patients characterized by hypoxemia and non-compliant lung. In this review, we discuss the pathophysiology of ARDS, including the mechanisms involved in the formation of pulmonary edema, the dysregulated inflammatory and immune responses, the activation of procoagulant events, the cellular communication by extracellular vesicles (EVs) between different types of cells and the interaction of the lung with other organs. Activation of inflammation, coagulation, and cell death processes result in the disruption of the alveolar-capillary membrane and the consequent protein-rich edema formation in the alveoli, in which structural and functional alterations of the alveolar epithelium play an essential role. Inflammation and activated endothelial cells trigger coagulation cascades and platelets that generate a procoagulant state in both the airspace and the intravascular compartment with the formation of fibrin in airspaces and thrombi in the microvasculature that aggravate alveolar injury and gas exchange. The crosstalk between epithelial/endothelial cells, platelets, and immune cells is mediated by EVs, whose role in the pathogenesis of ARDS is not known. Finally, the interaction of the lung with other organs has become an important determinant in the development and resolution of ARDS. Understanding the pathophysiological mechanisms involved in ARDS is crucial to developing new therapeutic strategies.

Keywords

Acute respiratory distress syndrome; Mechanisms; Pulmonary edema; Inflammation; Coagulation; Extracellular vesicles (EVs); Organ interaction

1. Introduction

Acute respiratory distress (ARDS) is a life-threatening condition in critically ill patients defined as the rapid onset of pulmonary edema not fully explained by cardiac failure or fluid overload, resulting in respiratory failure and hypoxemia. ARDS is an inflammatory lung injury characterized by acute onset, bilateral pulmonary infiltrates, poor oxygenation, and diffuse alveolar damage [1]. The leading causes of ARDS are pneumonia and non-pulmonary sepsis. Other causes of ARDS are the aspiration of gastric contents, major trauma (including burns or penetrating injuries), acute pancreatitis, hemorrhagic shock, ischemic insults, reperfusion injury, drug overdose, and transfusions [2, 3]. The infection by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), responsible for the current pandemic of coronavirus disease 2019 (COVID-19), has dramatically risen the ARDS incidence, which reaches nearly 40% of hospitalized patients and 75% of Intensive Care Unit (ICU) patients with COVID-19 pneumonia [4, 5].

The histological hallmark of ARDS is the diffuse alveolar damage (DAD), characterized by protein-rich edema, neutrophil accumulation into alveolar spaces, alveolar hemorrhage, fibrin deposition (due to the enhanced pro-coagulation), and hyaline membrane formation [2] (Fig. 1). However, not all patients clinically diagnosed of ARDS have the histological manifestation of DAD in the lung. Indeed, clinical reports before the SARS-CoV-2 pandemic indicate that DAD is only found in 56.4% of ARDS patients [6]. On the other hand, in postmortem studies in patients with ARDS, the presence of DAD has been associated with a different clinical profile compared to patients without DAD [2, 3, 5, 7].

ARDS is a common cause of death in critically ill patients, with a high mortality rate of 30–40% before the pandemic of SARS-CoV-2, reaching a mortality rate of 69–73% in COVID-19 patients with ARDS in some countries [8]. Although improvements in supportive care have been achieved during the last 30 years, no effective pharmacological treatment has been developed yet [9]. Moreover, ARDS often occurs in the setting of multiple organ failure, which in turn aggravates lung damage [10]. In addition, many studies have reported that ARDS survivors have a reduced quality of life as indicated by restrictive ventilatory deficits, significant exercise limitation, fatigue, muscle weakness, and neurocognitive and mood disorders [2, 11, 12]. Therefore, understanding the pathophysiological mechanisms responsible for ARDS development is crucial to developing new therapeutic strategies.

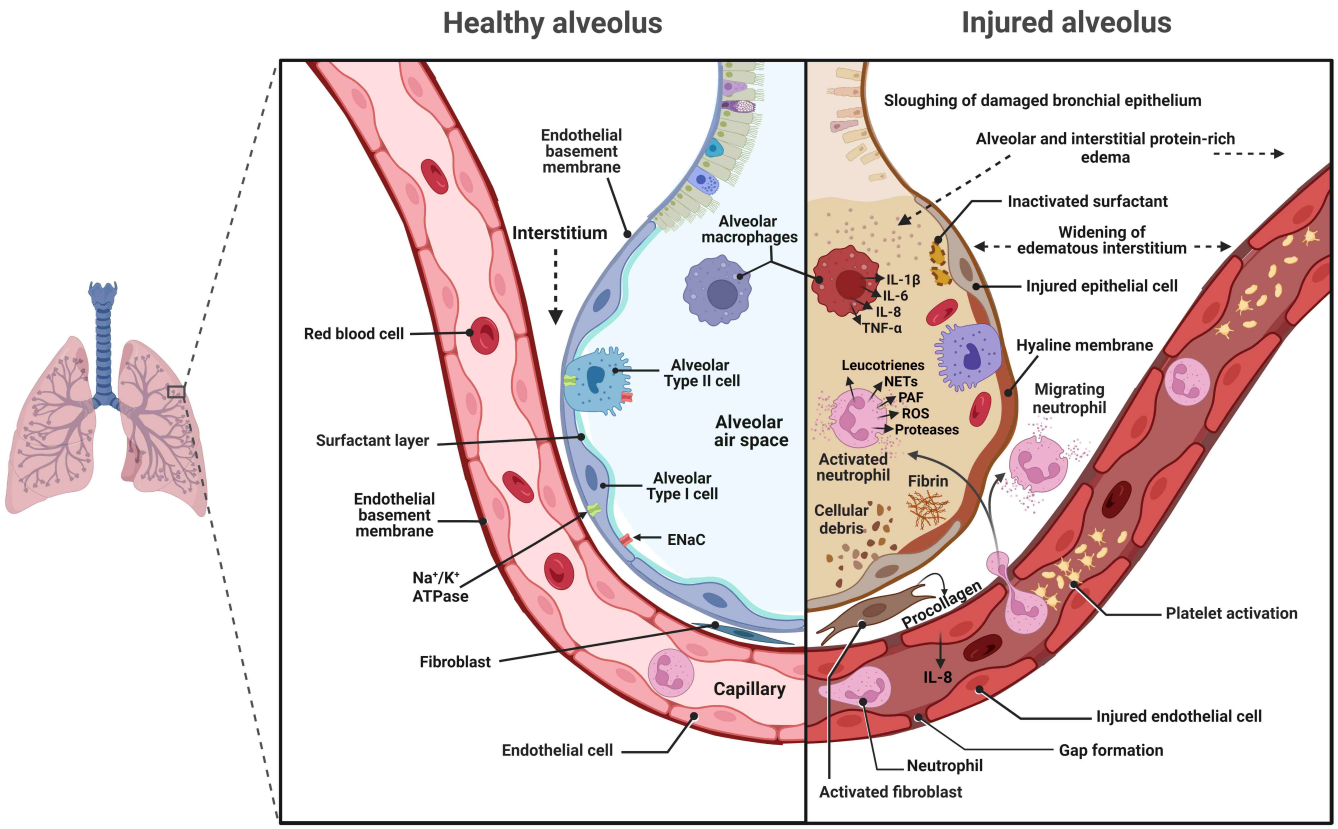

FIGURE 1. Characteristics of diffuse alveolar damage (DAD). The acute phase of DAD is characterized by alveolar epithelial and endothelial cell damage, an early increased permeability of the alveolar-capillary membrane, and flooding the airspace with protein-rich pulmonary edema fluid. Activation of resident alveolar macrophages and enhanced neutrophil migration and activation provide host defense, but they also release pro-inflammatory chemokines, cytokines, and other products (proteases, ROS, NETs) that can be deleterious. Platelet activation and release of vasoactive-procoagulant products lead to thrombi formation in the microvasculature and fibrin deposition in the alveolar airspaces, which contributes to the formation of hyaline membrane (mainly formed by deposition of proteins, fibrin, and cellular debris) on the denuded epithelial membrane. Activation of fibroblast leads to collagen deposition in the interstitium. Also, alveolar hemorrhage can occur, and the extravasated red blood cells can release cell-free hemoglobin, exacerbating injury via oxidant-dependent mechanisms. Figure created with BioRender.com. Na^+/K^+-ATPase, sodium/potassium adenosine triphosphatase; ROS, reactive oxygen species; NETs, neutrophil extracellular traps; PAF, platelet-activating factor; IL, interleukin; TNF, tumor necrosis factor.

2. Pathology of ARDS

The pathological findings in the lungs of patients with ARDS change over time, and the disease progression is variable. Although several phases have been described, they can occur concurrently [13]. The early exudative phase includes diffuse alveolar damage with disruption and loss of epithelial and endothelial cells, interstitial and alveolar flooding by protein-rich edema fluid, neutrophil and macrophage influx, and hemorrhage into the alveolar space. In the alveolar epithelium, type I cells can be irreversibly damaged, and the denuded space is replaced by hyaline membranes, while injury to the surfactant-producing type II cells contributes to alveolar collapse [14]. Because of endothelial damage and a procoagulant state, microthrombi form. In the subacute phase (the next 7–14 days), some of the edema has usually been reabsorbed, and proliferation of alveolar epithelial type II cells can take place associated with squamous metaplasia as a repairment mechanism of the alveolar epithelium. Although ARDS may resolve entirely in some patients at this point, in others it progresses to a fibroproliferative phase (after 14 days), in which there is infiltration of fibroblasts and more evidence of collagen deposition and remodeling of the interstitial and alveolar spaces [13, 15, 16]. In this chronic phase, there is a resolution of the acute neutrophilic infiltrate and more evidence of fibrosis, while alveolar epithelial proliferation can still progress. The persistence of fibroblast activation and collagen deposition can lead to lung fibrosis, which in some cases is irreversible.

3. Pathophysiological mechanisms of ARDS

ARDS is characterized by a dysregulated inflammatory response resulting in enhanced leukocyte infiltration into the alveolar space, a procoagulant state, and epithelial and endothelial cell damage that results in an enhanced permeability of the alveolar-capillary membrane. This increased perme-

ability leads to protein-rich edema formation in the alveolar and interstitial spaces in contrast to the low protein pulmonary edema that results from hydrostatic causes such as congestive heart failure [17–19].

4. Pulmonary epithelial/endothelial injury and edema in ARDS

In ARDS, a pulmonary protein-rich edema is an early event that markedly contributes to hypoxemia in these patients. Alterations in alveolar fluid transport and clearance and the increase in endothelial/epithelial permeability lead to alveolar proteinaceous edema. Multiple factors, including dysregulated inflammation, intense leukocyte infiltration, activation of procoagulant processes, cell death, and mechanical stretch, contribute to the disruption and dysfunction of both epithelial and endothelial barriers [17–19].

4.1 Pulmonary epithelial injury

In healthy conditions, the alveolar-epithelial barrier is intact and maintains its capability of alveolar fluid clearance, allowing the reabsorption of excess alveolar fluid. This absorption of alveolar fluid from the airspaces to the interstitium is carried on by a vectorial ion transport, mainly mediated by the apical epithelial sodium channels (ENaC) and the basolateral sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase) pumps (Fig. 2) [20]. Some factors such as influenza infection, hypoxia, or hypercapnia can diminish the function of these sodium channels and Na^+/K^+-ATPase pumps, resulting in a reduced capacity of fluid clearance in the lung of patients with ARDS [2, 21, 22].

Activation of cell death mechanisms during ARDS, such as FasL (Fas Ligand)-mediated apoptosis or pyroptosis (highly inflammatory type of programmed cell death), are responsible for the loss of alveolar epithelial cells, thus contributing to barrier hyperpermeability [23–25]. Cell death can be triggered on epithelial cells by direct injury on the epithelium or activation of the pattern recognition receptors (PRRs). These PRRs are cell-surface or cytosolic proteins activated by the pathogen-associated molecular patterns (PAMPs) and/or damage-associated molecular patter (DAMPs). PAMPS are extrinsic molecules derived from various microorganisms, while DAMPs are intrinsic molecules derived from injured cells or extracellular molecules. Toll-like receptors and the receptor for advanced glycation end products (RAGE) are examples of PRRs. Besides apoptosis, activation of alveolar epithelial PRRs activates inflammatory cascades that alter the alveolar epithelial and endothelial barriers. Internalization of the PRRs upon pathogen binding, for instance, releases new particles of pathogens, inflammatory molecules (*e.g.*, cytokines), DAMPs, and PAMPs into the alveolar space that can exert a deleterious effect on the epithelial integrity and function [26, 27].

Alterations in cell-cell adhesion in the alveolar epithelium and its interaction with extracellular matrix (ECM) have also been reported in ARDS. Intercellular junctions of epithelial cells are mediated by tight junctions (TJs) complexes, which consist of some transmembrane proteins such as junctional adhesion molecules (JAMs), occludin, and claudins that interact with the adaptor protein zonula occludens (ZO), which, in turn, binds to the actin fibers of the cytoskeleton (Fig. 2). These TJ-actin complexes are essential structures in alveolar epithelial permeability since they control cell tension and contraction and the paracellular transport of fluid and solutes into the airspace [19] (Fig. 2). Therefore, dysfunction of the TJs results in increased permeability to water and proteins and deterioration of the capacity of alveolar fluid clearance of the epithelium, leading to the formation and perpetuation of lung edema. Studies in experimental models of acute lung injury indicate massive changes in the expression and localization of ZO and claudins with the consequent increase in epithelial permeability [25, 28, 29]. The ECM represents the scaffold of alveolar epithelium and capillary endothelium that participates in cell-cell adhesion, and in the fluid trafficking into the airspace and cell signaling. In ARDS, the oxidative stress and the dysregulated inflammation in the lung induce the expression of some enzymes, such as elastases or matrix metalloproteinases (MMPs), that change the structure and stiffness of the ECM and, consequently, modify the expression of the TJ proteins and barrier function, contributing to lung edema formation [19, 30–32].

Alveolar inflammation is characterized by marked neutrophil influx, activation of alveolar macrophages, and release into the airspaces of cytokines (tumor necrosis factor-α (TNF-α), tumor necrosis factor receptor (TNFR), interleukin-1β (IL-1β), interleukin-1 receptor antagonist (IL1RA), IL-6, interferon-γ (INF-γ), granulocyte colony-stimulating factor (G-CSF), transforming growth factor-β (TGF-β)) and chemokines ((IL-8, epithelial neutrophil-activating protein 78 (ENA-78), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-2 (MIP-2)) by alveolar endothelial, epithelial, and immune cells [19, 33]. Among them, TGF-β is a key mediator in ARDS that can be detected in bronchoalveolar lavage (BAL) fluid from patients with ARDS in the first 24 h of diagnosis and has an essential role in its onset and progression. In the early phase, TGF-β causes apoptosis in alveolar epithelial cells and contributes to lung edema by increasing permeability and decreasing the alveolar fluid clearance of the alveolar epithelium [34]. This decrease in the alveolar fluid clearance is due to changes in the expression of apical epithelial sodium channels (ENaC) and the basolateral Na^+/K^+-ATPase pumps [14, 19, 35]. In a later stage, TGF-β exerts an essential role in regulating inflammation, immunity, tissue repair, and fibrosis. In this line, TGF-β contributes to lung fibrosis via activation of lung fibroblasts and indirectly via inducing apoptosis of alveolar epithelial cells [34, 36].

4.2 Pulmonary endothelial injury

Alteration of the vascular endothelial function and extensive alveolar-capillary leak also occurs in the lung of patients with ARDS. Endothelial injury can be caused by the adhesion and migration of neutrophil granulocytes on and through the endothelium [37] and by the direct effects of cytotoxic factors present in the intravascular and the intra-alveolar compartments. This contact between intra-alveolar factors and the

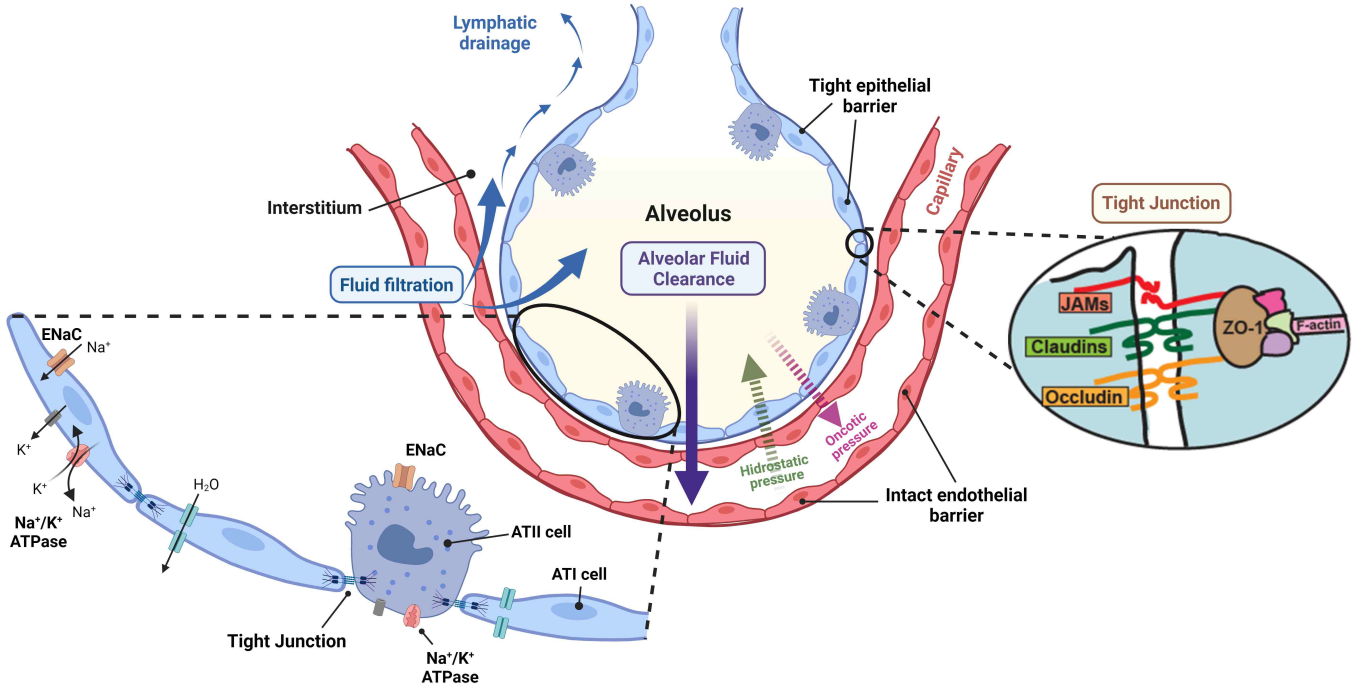

FIGURE 2. Role of alveolar epithelium in lung edema. The alveolar epithelium is a continuous and tight monolayer of alveolar type I (ATI) and alveolar type II (ATII) cells. ATI cells are very thin and permit gas exchange, and ATII cells produce surfactant to enable lung expansion with low surface tension. The intact alveolar epithelium is linked by intercellular tight junctions that restrict the passage of water, electrolytes, and small hydrophilic solutes to the airspaces. In the normal lung, the transvascular flux of fluid out of the capillary moves water and low-molecular-weight solutes into the interstitial space depending on the permeability of the capillary membrane and the net difference between hydrostatic and protein osmotic pressure. In health, this fluid does not cross the epithelial barrier and moves into the lymphatics. When alveolar edema occurs, this edema fluid accumulating in airspaces is absorbed by the epithelium following a transepithelial osmotic gradient created by an active sodium transport. This sodium gradient is created and maintained by the apical membrane epithelial Na^+ channels (ENaC) and the basolateral sodium/potassium adenosine triphosphatase (Na^+/K^+-ATPase) in both ATI and ATII cells, causing excess water to move passively from the airspaces to the interstitium. Figure created with BioRender.com.
JAMs, junctional adhesion molecules; ZO-1, Zonula occludens-1.

endothelium occurs because of the disruption of the alveolar epithelial barrier. Many intravascular and intra-alveolar factors activate cell death mechanisms on endothelial cells, such as apoptosis and pyroptosis, and contribute to the breakdown of endothelial intercellular junctions [38, 39], leading to an increase in vascular permeability that contributes to lung edema and respiratory failure in these patients [2].

Like alveolar epithelial cells, endothelial cells can be activated by PAMPs and DAMPs, some of them derived from alveolar epithelial cells and resident macrophages, as well as from circulating leukocytes and platelets, such as TNF-α, IL-1β, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), platelet-activating factor (PAF), TGF-β1 and angiostatin (a cleavage product from plasminogen with an intense antiangiogenic activity) that are increased in the BAL fluid of patients with ARDS [34, 40, 41]. Among these factors, TNF-α, TGF-β, and angiostatin contribute to endothelial injury by inducing apoptosis [42–44]. In addition, TGF-β contributes to increased endothelial permeability via phosphorylation of adherent junction proteins and the formation of stress actin fiber in endothelial cells *in vitro* [45]. TNF-α also disrupts tight junction proteins (ZO-1, claudin 2-4-5) and β-catenin in pulmonary endothelial and epithelial cell layers, which can be exacerbated by IFN-γ [28, 46, 47]. Il-1β increases alveolar endothelial and epithelial permeability via Ras homolog family member A (RhoA)/integrins-mediated epithelial TGF-β release [48].

Activated endothelial cells trigger a cascade of events, including activation of coagulation cascades, activation and aggregation of platelets, formation of platelet-leukocyte aggregates, and up-regulation of cell adhesion molecules, such as P-selectin, E-selectin, ICAM (intercellular adhesion molecule) and VCAM (vascular cell adhesion molecule), that mediate leukocyte adhesion and transmigration across the endothelium (Fig. 3). This transmigration of leukocytes, the deposition of platelets and neutrophils on endothelium, or the formation of platelet-neutrophil aggregates play a synergic role in increasing vascular permeability in the lung [39, 49] (Fig. 3).

Elevated levels of angiotensin II (AngII) have been found in the lung of patients with ARDS. AngII interacts with Ang II receptor type 1 (AT1R), mainly expressed in the endothelium, and induces the production of several mediators (inflammatory cytokines, eicosanoids, and VEGF) that trigger proinflammatory responses and elevate the pulmonary vascular permeabil-

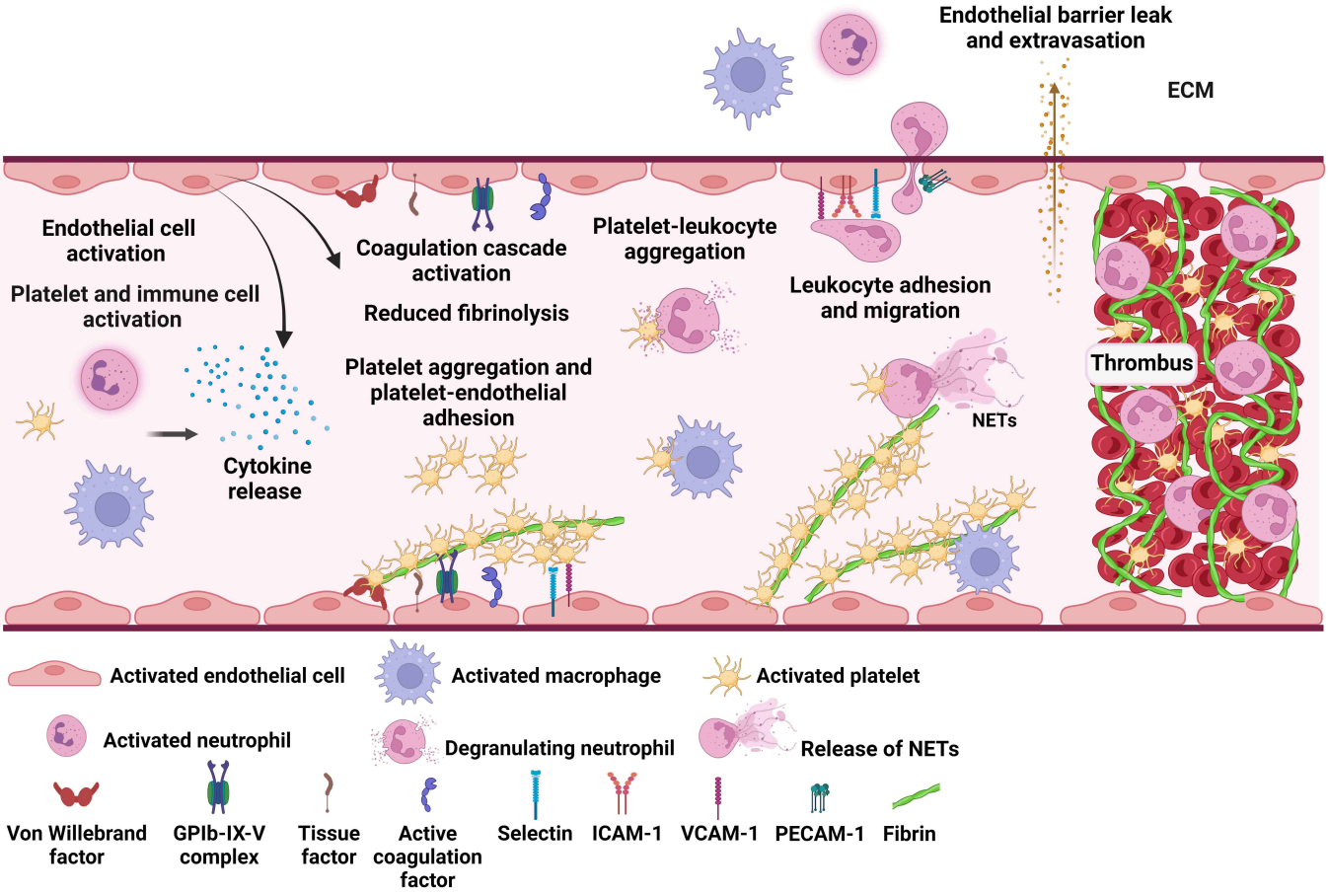

FIGURE 3. The inflammation and coagulation interaction in ARDS. Activated endothelial cells trigger various events that include activation of the coagulation cascade (with reduction of anticoagulant and fibrinolytic factors), the release of cytokines, and up-regulation of leukocyte and endothelial cell adhesion molecules (P-selectin, E-selectin, ICAM, VCAM, PECAM). These events, in turn, promote activation of leukocytes and platelets that leads to platelet aggregation and formation of platelet-leukocyte aggregates, facilitating the adhesion and migration of leukocytes to the interstitium and alveolar airspaces. In addition, the generation of tissue factor (from exposed subendothelium or released by activated macrophages/monocytes and platelets) and von Willebrand factor (vWF) (released by activated endothelial cells and platelets) mediates further platelet adhesion and aggregation. Activated neutrophils release pro-inflammatory mediators (chemokines, cytokines) along with ROS, enzymes (MMPs, elastase, myeloperoxidase), and neutrophil extracellular traps (NETs) that have an essential role in host defense but cause endothelial and epithelial injury under overwhelming pathological conditions. Coagulation and activated platelets and leukocytes augment microvascular endothelial damage leading to the disruption and increased permeability of the endothelial barrier. All these events facilitate further movement of inflammatory cells and protein-rich fluid into the interstitium and alveoli. In the intravascular compartment, activation of coagulation, platelets, leukocytes, and endothelial cells, along with the generation of thrombin and fibrin, leads to the formation of thrombi in the pulmonary microvasculature. Figure created with BioRender.com.
ECM, extracellular matrix; ROS, Reactive Oxygen Species; MMPs, Matrix Metalloproteinases; NETs, Neutrophil Extracellular Traps; GPIb-IX-V, glicoprotein Ib-IX-V; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion protein 1; PECAM-1, platelet-endothelial cell adhesion molecule-1.

ity, contributing to pulmonary edema [50, 51]. Interestingly, SARS-CoV-2 is internalized by alveolar epithelial cells via binding to angiotensin-converting enzyme 2 (ACE2) receptor, resulting in an ACE2 downregulation and the subsequent up-regulation of angiotensin II (Ang II) that contribute to lung endothelial vascular dysfunction in COVID-19 pneumonia [52].

Besides TJs, endothelial cells are also connected by adherens junctions, which contain vascular endothelial cadherin (VE-cadherin) that links to the actin cytoskeleton. The weakening of endothelial junctions induced by inflammation also relies on the destabilization of VE-cadherin contacts and alterations in the endothelial actin-myosin cytoskeleton [39].

Altogether, the increase in endothelial and epithelial permeability leads to protein-rich edema formation in the lung, resulting in the alteration of gas exchange and the subsequent hypoxemia in ARDS. Extensive alveolar epithelium damage has been observed in non-surviving ARDS patients, whereby the degree of alveolar epithelial damage seems to determine the ARDS severity and prognosis [2, 53].

5. Humoral and cellular immune system in ARDS

5.1 Activation of pattern recognition receptors

In the lung, activation and regulation of innate and adaptive immunity are mediated by patter recognition receptors (PRRs), also present in alveolar epithelial and endothelial cells as mentioned above [27]. Activation of these PRRs by PAMPs and DAMPs leads to nuclear translocation of transcription factors such as nuclear factor (NF)-κB, predominantly through a myeloid differentiation primary response gene 88 (MyD88)-dependent mechanism. This is followed by the transcription of proinflammatory cytokines such as TNF-α, IL-1β, and IL-8, which can activate immune cells and alter alveolar epithelial and endothelial functions in the lung. This early humoral and cellular immune activation contributes to lung injury and widespread lung inflammation to other organs, promoting multi-organ damage [54].

5.2 Innate immune cells

5.2.1 Activation of M1 macrophages

Two types of activated macrophages have been described, the M1 proinflammatory phenotype and the M2 anti-inflammatory. The M1 polarization of resident alveolar macrophages represents one of the local defenses against pathogens. In this stage, M1 alveolar macrophages trigger pathogen clearance mechanisms and release reactive oxygen species (ROS) and proinflammatory cytokines (IL-1β, IL-6, IL-18, MCP-1, MIP-2, and TNF-α) that activate and recruit immune cells to the site of infection, including natural killer cells, cytotoxic T cells, and innate lymphoid cells. These cells are primed and increase their cytotoxicity activity against the pathogen, partially mediated by the production of IFN-γ. These immune cells release a second wave of cytokines, acting as chemoattracts of circulating monocytes and neutrophils [55, 56] that can be cytotoxic for the alveolar-capillary membrane. To assist in the clearance of viral, bacterial, or fungal pathogens, resident and recruited neutrophils release molecules, such as myeloperoxidase (MPO), metalloproteinases (MMPs), elastase, and neutrophil extracellular traps (NETs), that can alter the structure and function of the alveolar epithelial/endothelial barrier and ECM [57].

In ARDS, the immune response is dysregulated, and M1 alveolar macrophages release high levels of proinflammatory cytokines (IL-1β, IL-6, IL-2, IL-7, and IL-8, TNF-α) and chemokines (MCP-1, MIP-1α), resulting in infiltration of immune cells (mainly circulating monocytes and neutrophils) [58, 59]. Although the early polarization of macrophages to M1 has an initial protective function against pathogen infection, growing evidence demonstrates that both resident and recruited M1 macrophages play a relevant role in ARDS pathogenesis. Indeed, experimental models of acute lung injury have reported reduced mortality when inhibitors of M1 polarization were administered [60–63].

5.2.2 Activation of M2 macrophages

The polarization of M1 macrophages to M2 phenotype is induced to counteract the proinflammatory stage. M2 macrophages play a relevant role in inflammation resolution and lung tissue repair by clearance of cellular debris and apoptotic cells, limiting proinflammatory cytokine release and inducing the expression of anti-inflammatory mediators (IL-10, fibronectin 1, TGF-β), which reduce levels of nitric oxide synthase and nitric oxide species via arginase 1 induction [64]. In this regard, the administration of M2 alveolar macrophages to mice with lipopolysaccharide (LPS)-induced acute lung injury depletes circulating monocytes, reduces neutrophil infiltration and oxidative stress, and decreases the levels of inflammatory molecules (TNF-α, IL-1β, and IL-6), elevates the expression of anti-inflammatory mediators (IL-17, MCP-1, IL-10), and increases levels of regulatory T-cells (Treg) [65]. Apart from balancing the pro- and anti-inflammatory cytokines levels, M2 macrophages also recognize and phagocytize neutrophils, reducing and preventing their cytotoxic effects on the lung [64].

Finally, the late and complicated phase of ARDS, known as the fibro-proliferative phase, is characterized by excessive fibroblast proliferation and increased ECM deposition. Numerous studies have reported that persistently activated M2-macrophages also participate in this phase of ARDS [64, 66]. In this regard, persistently activated M2-macrophages release TGF-β, fibronectin, proline, and tissue inhibitors of metalloproteinase (TIMP) that promote fibroblast proliferation and hamper the removal of excessive ECM. On the other hand, M1-macrophages have been reported to play an anti-fibrotic role in this phase by producing antifibrotic cytokines (*e.g.*, CXCL10) and MMPs capable of degrading the excessive ECM [67]. Therefore, in this late phase of ARDS, the M1/M2 macrophage balance in the microenvironment of the injured lung seems crucial for ARDS resolution.

5.2.3 Neutrophil activation

The activation of neutrophils into alveolar space releases ROS that triggers oxidative stress and intracellular enzymes (MMPs, elastase) that degrade the ECM, contributing to alveolar epithelial barrier disruption [31, 68]. In addition, neutrophils can undergo NETosis, a type of cell death by which neutrophils extrude NETs. NETs are composed of DNA fibers, histones, and antimicrobial proteins, in which pathogens are immobilized and exposed to a local high and lethal concentration of effector proteins [69]. An excessive NET formation enhances a proinflammatory response that alters endothelial and epithelial barriers mainly by decreasing ZO-1, VE-cadherin, and β-catenin [70, 71]. Moreover, *in vitro* assays have shown the role of NETs as a scaffold for platelets, red blood cells, and procoagulant factors (such as von Willebrand factor and tissue factor), contributing to thrombus formation and propagation [72, 73]. Indeed, elevated plasma levels of NETs in humans have been associated with ARDS severity and mortality [74].

5.3 Adaptive immune cells

During infection, the adaptive immune response is rapidly initiated. Pathogen particles are presented through major his-

tocompatibility complex class I (MHC I) of activated dendritic cells (DC) to CD8+ T cells. The latter cells are cytotoxic and induce apoptosis on infected cells by producing perforin and granzymes. Activated CD8+ T cells also become pathogen-specific effectors and memory T cells. The major histocompatibility complex class II (MHCII) is presented by DCs to CD4+ T cells. Then, CD4+ T cells may differentiate into one of several T helper (Th) cell lineages, including Th1, Th2, Th17, and T follicular cells, as defined by their pattern of cytokine production and function. Th1, Th2, and Th17 cells contribute to pathogen clearance, whereas T follicular cells assist B cells in the production of neutralizing antibodies [56].

Alterations in adaptive immune response have been broadly described in ARDS. For example, levels of CD4+ T cells are dramatically reduced in patients with sepsis-induced ARDS, as well as the Th1 and Th2-associated cytokine production and pathogen clearance [75]. In contrast, Th17 cells are elevated in the lung [76], BAL fluid [77], and blood [78] of ARDS patients and experimental animals after acute lung injury. Differentiation to Th17 is mainly induced by IL-6, which is elevated in ARDS. Th17 cells activate macrophages, DCs, and neutrophils, triggering the release of proinflammatory cytokines (IL-1, IL-6, IL-8, IL-21, IL-17A, TNF-α, and MCP-1) by these cells [78], which is accompanied by increased alveolar epithelial permeability [76] and greater severity of illness [77].

Another subtype of CD4+ T cells, the regulatory T (Treg) cells, are also altered during ARDS. Treg cells exert an anti-inflammatory effect that is essential in resolving lung injury. They suppress the effector T+ cell responses (mainly from Th17 cells) and maintain the tolerance to self-antigens, avoiding autoimmune responses [79]. During acute lung injury, the increased levels of IL-6 enhance Th17 cell activation and Treg suppression, altering Th17/Treg balance [80]. The Th17/Treg ratio increases in mild to severe ARDS patients and has been proposed as a predictor biomarker of mortality in ARDS, correlating with increased APACHE (Acute Physiology and Chronic Health disease Classification System), SOFA (Sequential Organ Failure Assessment) and lung injury scores [81]. Interestingly, increasing Treg levels via stimulation of the cAMP/FOXP3 (cyclic adenosine monophosphate/ forkhead box P3) signal reduces the number of Th17 cells protecting against lung injury and mortality in mice with acute lung injury [82].

6. Hemostatic and immune system interaction

ARDS is characterized by an imbalance between coagulation and the immune system. Activation of procoagulant factors along with an impaired anticoagulant system leads to reduced fibrinolysis, a massive production of thrombin, and, consequently, an intra-alveolar and lung intravascular fibrin formation. A cross-talk between coagulation and the innate immune system initiates the complex process of immunothrombosis, which exerts a vital role as a host defense mechanism [83]. In ARDS, immunothrombosis is dysregulated, leading to excess formation of immunologically mediated thrombi that affect the lung microvasculature (Fig. 3). Therefore, the restoration of the alveolar and intravascular hemostasis and the adequate control of immune responses are crucial in the pathogenesis of ARDS [84–87].

Immunothrombosis is the consequence of endothelial, platelet, and innate immune cell activation, excessive coagulation, and decreased fibrinolysis (Fig. 3) [84]. It has been shown that patients with ARDS have increased levels of fibrinopeptide A, a direct marker of thrombin generation, and soluble thrombomodulin (probably degraded from alveolar epithelial thrombomodulin), and decreased levels of the anticoagulant activated protein C (APC) in their alveolar airspaces and plasma. On the other hand, there is suppression of the fibrinolysis in the alveoli caused by increased levels of plasminogen activator inhibitor-1 (PAI-1) produced by endothelial cells and mediated by inflammation. Increased levels of PAI-1 are present in bronchoalveolar fluid and plasma from patients with ARDS. PAI-1 suppresses tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA) from converting plasminogen to plasmin, which ultimately leads to reduced fibrin degradation [86, 88–93].

6.1 Endothelial damage

In injured alveoli, endothelial damage activates innate host responses and coagulation, promoting platelet activation and aggregation (Fig. 3). After endothelial damage, disruption of the intercellular junctions exposes the subendothelial extracellular matrix containing the procoagulant tissue factor (TF). TF is also produced by endothelial and epithelial cells in the alveoli and by activated macrophages/monocytes and platelets. Then, TF binds to Factor VII to initiate TF-dependent coagulation, resulting in thrombin generation, platelet aggregation, conversion of fibrinogen to fibrin, and, consequently, formation of blood clots (Fig. 3) and fibrin deposition in the alveolar airspaces [94, 95]. The von Willebrand factor (VWF), produced by activated endothelial cells, platelets, or exposed subendothelium, mediates further platelet adhesion and aggregation [92]. Under activation, vascular endothelial cells express cell adhesion proteins such as P-selectin, E-selectin, ICAM, and VCAM that enable the recruitment of platelets and leukocytes, which also have a pivotal role in hemostasis and thrombosis [96] (Fig. 3). In addition, the renin-angiotensin pathway plays an essential role in ARDS promoting coagulation. Accumulation of angiotensin II (AngII) has been observed in the lung of patients with ARDS. The binding of AngII to angiotensin II receptor type 1 (AT1) augments pulmonary vasoconstriction and contributes to TF and PAI-1 expression on platelets and endothelial cells [97].

6.2 Platelet activation and interaction with immune cells

Platelets are an essential component of ARDS pathogenesis. In a small human study, platelet activation was greater in ARDS patients than in healthy controls [98]. Also, it has been shown that the severity of lung injury is tightly correlated with platelet-derived α-granule mediators in BAL fluid [99]. Platelets have an essential function in coagulation and the innate immune system, participating

in neutrophil and monocyte activation and recruitment (Fig. 3). During endothelial damage, the exposure to subendothelial collagen leads to platelet activation and subsequent release of cell membrane proteins and granular contents, including chemokines, cytokines (IL-1, TNF-α), coagulation proteases, adhesive molecules, growth factors, and mediators of angiogenesis that cause further platelet activation and amplification of the innate immune responses [100–102]. Activated platelets bind to leukocytes, such as neutrophils and monocytes, promoting their activation, adhesion, and migration at the site of injured endothelium via expression of adhesion molecules, such as ICAM-1 and VACM-1 (Fig. 3). Also, leukocyte rolling on vascular endothelium is facilitated by platelet-derived P-selectin and thromboxane-A2, facilitating leukocyte migration into injured tissue (Fig. 3). This platelet-neutrophil binding is mediated by toll-like receptor 4 (TLR4) engagement and participates in neutrophil activation and release of NETs [103]. Although NETs show antimicrobial properties by trapping and inactivating microorganisms in blood vessels, they also have procoagulant properties and might cause collateral tissue damage, in which the neutrophil-derived proteases have an important role. Furthermore, NETs cause platelet activation and aggregation, and activates coagulation pathway, contributing to fibrin formation [103–105]. Also, activated platelets exert an important function in immune defense by releasing antimicrobial peptides (*e.g.*, AMPs) and enhancing the phagocytosis capacity of leukocytes, however, an increased formation of the platelet-leukocyte complex contributes to acute lung injury and other organ failure [106]. Actually, preclinical studies of acute lung injury (ALI) show that the depletion of platelet leads to a significant reduction of neutrophil recruitment in the lung, and that the inhibition of platelet-neutrophil complex improves gas exchange and prolongs animal survival [107].

6.3 Molecular link between hemostatic and immune systems

Immune cells as well as platelets and endothelial cells can be activated by factors of the coagulation cascade. The molecular link between hemostatic and immune systems is mainly based on the protease activated receptors (PARs) on immune cells, platelets, and endothelial cells. Complexes of TF/Factor VIIa (TF/FVIIa), TF/FVIIa/Factor Xa (TF/FVIIa/FXa) and Factor Xa and thrombin trigger PARs, which activate innate immune cells and the expression of cytokine and adhesion molecules. These effects enhance inflammatory processes in the lung, including P-selectin-mediated leukocyte migration, that cause disruption of endothelial barrier by altering endothelial cytoskeleton and further platelet activation [83, 92, 108, 109]. In addition, fibrinogen and fibrin can directly initiate the activation of neutrophils [110].

On the other hand, inflammation facilitates and enhances coagulation. In this regard, proinflammatory cytokines activate coagulation system and also play an important role in the down-regulation of physiological anticoagulant pathways [111]. Inflammatory cytokines, such as IL-1, TNF-α, IFN-γ, and lipopolysaccharide (LPS) of gram-negative bacteria, known to be elevates in ARDS patients, induce TF expression on macrophages and platelets [84]. IL-2, also elevated in these patients, decreases fibrinolysis by upregulating of the antifibrinolytic PAI-1. Interestingly, it has been shown that platelets have receptors for IL-1β, IL-6 and IL-8. These cytokines that are one of the most reported elevated cytokines in ARDS have the capability of activating and spreading platelets [112]. IL-6 and IFN-γ also increases the expression of TF on endothelial cells and monocytes and can impair vascular endothelium function. The chemokines, such as IL-8, have an indirect prothrombotic effect via attracting neutrophils to the site of infection [84, 101]. As mentioned before, the release of NETs by neutrophils can contribute to tissue damage by exacerbating local inflammation and enhancing microvascular thrombosis in the lung. This organized recruitment of innate cells and platelets at the site of endothelial injury, in turn, leads to the release of pro-inflammatory mediators contributing to further activation of intravascular immune responses [84, 113].

6.4 Hypoxia enhances immunothrombosis

Finally, hypoxia occurs in moderate-to-severe ARDS and this can lead to endothelial dysfunction, including disruption of vascular tone and hypercoagulability. Hypoxia-induced expression of adhesion molecules P-selectin, E-selectin, ICAM-1 and VCAM-1 that results in platelet and leukocyte recruitment and more expression of TF, causing hypercoagulability [114, 115]. Under hypoxia, endothelial and immune cells release hypoxia-induced factors (HIFs), a transcription factors that promote thrombosis by increasing endothelial release of PAI-1 and inflammatory cytokines (TNF-α, IL-2) and by downregulating thrombomodulin [114–116]. In macrophages, HIFs promote their activation and local aggregation, with the consequent release of proinflammatory cytokines, including IL-6 and TNF-α [116].

Altogether, immunothrombosis in the lung results in the formation of an intravascular scaffold, enhancing the recognition and destruction of pathogens and supporting endothelial integrity. However, uncontrolled immunothrombosis might induce collateral tissue damage and contribute to ARDS and multiorgan dysfunction.

7. Intercellular communication mediated by extracellular vesicles (EVs)

Extracellular vesicles (EVs) are membrane-bound vesicles that mediate intercellular communication by transferring proteins, genetic material, and organelles between cells in both physiological and pathological conditions [117]. A growing body of evidence demonstrates the role of EVs in the pathogenesis of ARDS by modulating the onset and the progression of alveolar inflammation, coagulation, and epithelial/endothelial barrier dysfunction.

During lung injury, EVs derived from structural (endothelial and epithelial cells) and immune cells carry proinflammatory cytokines and chemokines (such as TNF-α, IL-6, IL-8, IL-1β, CXCL1, CXCL-10, MCP-1, MIP-2) capable of activating and recruiting immune cells into alveolar space, which exacerbate

alveolar damage [118]. Moreover, these pro-inflammatory EVs can reach epithelial and endothelial cells and contribute to direct alteration of the alveolar-capillary membrane, increasing lung permeability by mechanisms involving apoptosis and weakening intercellular TJ complexes [119–121]. During lung injury, EVs derived from activated monocytes, neutrophils and platelets upregulate the adhesion molecules VCAM, ICAM, or/and CCL5 (C-C motif chemokine ligand 5) on endothelial cells, promoting and enhancing the adhesiveness of these immune cells to the endothelium [39]. The proinflammatory stimulus on platelets, endothelial cells, and alveolar epithelial cells also induced the release of EVs enriched on TF, which initiates the coagulation cascade and results in thrombin generation, fibrin deposition, and clot formation [122–124].

After the injury, alveolar epithelial cells release EVs enriched in IL-6 and MMP-1 that can be uptaken by nearby epithelial cells, contributing to pulmonary inflammation, degradation of ECM, and epithelial barrier disruption [125, 126]. Alveolar epithelial cell-derived EVs also transfer their cargo to immune cells un lung injury. Specifically, EV-mediated transfer of caspase-3 from epithelial cells to macrophages has been reported, resulting in the activation of macrophages and their secretion of proinflammatory molecules such as TNF-α, IL-6, and MIP-2 [127]. Epithelial cell-derived EVs can also activate NF-κB signaling on alveolar macrophages upon upregulation of TLR2, Myd88, TNF-α, and IL-6. Experimental models of acute lung injury also reveal the role of epithelial cell-derived EVs in triggering the migration of macrophages into the lung. In this regard, epithelial cell-derived EVs transfer several microRNAs such as miR-17, miR-221, miR-320a, miR-22, and miR-342 to macrophages, resulting in the expression of integrin β1 onto macrophage surface, which promotes macrophage adhesion and migration. This miRNA transfer also mediates macrophage secretion of TNF-α and NF-κB activation, further exacerbating lung inflammation in ARDS [128]. Importantly, it has been found that EVs derived from alveolar epithelial cells in ARDS patients are enriched in TF, highlighting the contribution of epithelial cells to the coagulation disorder occurring in these patients [123].

Experimental models of ALI/ARDS have also demonstrated the contribution of EVs derived from activated macrophages to lung injury by triggering inflammation. Under proinflammatory stimuli, macrophages release EVs enriched in TNF-α, IL-1β, and IL-6, which can be uptaken by alveolar epithelial cells and upregulates ICAM-1, IL-8, and MCP-1 expression. Macrophage-derived EVs also contain miRNAs, such as miR-223, capable of triggering monocyte differentiation into macrophages [129]. Activated macrophages also communicate with endothelial cells, activating ERK1/2 (extracellular signal-regulated kinase 1/2) and NF-κB signaling pathways and expressing the endothelial-leukocyte adhesion proteins VCAM-1, ICAM-1, and E-selectin, which promote leukocyte adhesion to endothelium and increase endothelial barrier permeability [130–132]. Importantly, this EV-mediated interaction between monocytes and endothelial cells also promotes intravascular activation of coagulation while reducing the anticoagulant properties of the vascular luminal surface of the endothelium. These events mainly occur by increasing TF and decreasing the levels of anticoagulant tissue factor pathway inhibitor (TFPI) and thrombomodulin in endothelial cells [130].

Several studies on experimental models of acute lung injury have shown that endothelial cell derived EVs induce changes in vascular permeability and modulate immune cells responses. Endothelial derived-EVs can transfer nitrated sphingosine-1-phosphate receptor 3, a critical molecule involved in vascular permeability, and Src kinase that impairs adherens junction and cytoskeleton integrity of targeted endothelial cells by mechanisms involving phosphorylation of myosin light chains and vascular endothelial-cadherin (VE-cadherin) [133–137]. Endothelial cell-derived EVs also target and activate macrophages, inducing the macrophage production of proinflammatory molecules (CXCL10, CCL4, CCL5, IL-6, IL-8, MCP-1) and increasing macrophage adhesiveness to the endothelium [138]. Endothelial cell-derived EVs have also been reported to target neutrophils and induce NET formation in mice with abdominal sepsis [136, 137]. In addition, increasing evidence reveals that endothelial cell-derived EVs have a relevant role in coagulopathies. Elevated plasma levels of pro-coagulant endothelial-cell derived EVs containing TF have been found in patients with sepsis [139], influenza A infection [140], and COVID-19 [141], which are associated with severity and mortality. In addition, in patients with sepsis, these elevated levels of TF on circulating endothelial-derived EVs correlate with the severity of sepsis and disseminated intravascular coagulation (DIC) [139].

As occurs in other types of cells, neutrophils release EVs whose content varies depending on the stimuli received, exerting distinct properties such as anti-inflammatory, proinflammatory, antibacterial, or procoagulant effects [142, 143]. Regarding the protective effects, neutrophil-derived EVs have been reported to specifically transfer miR-223 to alveolar epithelial cells, reducing the alveolar permeability and inflammatory cytokines (IL-6, IL-1β, CXCL1) in a mouse model of ventilator-induced lung injury [121]. Neutrophil-derived EVs can also reach macrophages and induce M1 or M2 macrophage polarization. In this regard, a study of acute lung injury in mice has shown that neutrophil-derived EVs contain proinflammatory molecules (such as miR-1260, miR-1285, miR-4454, and miR-7975) that induce proinflammatory M1 macrophage polarization. On the contrary, these EVs can contain anti-inflammatory miRNAs (miR-126, miR-150, and miR-451a) that promote the macrophage polarization to the M2-anti-inflammatory phenotype [144]. Neutrophil-derived EVs also exert proinflammatory effects on endothelial cells, enhancing the adhesiveness to leukocytes and platelets [145, 146], and increasing vascular permeability due to their content of cathepsin G, S100A-8, and S100A-9 [147]. In addition, proinflammatory neutrophil-derived EVs transfer arachidonic acid to platelets, resulting in increased production of thromboxane that contributes to platelet activation and aggregation [148]. Because of their content in enzymes, such as elastase and MMPs, neutrophil-derived EVs also mediate the degradation of ECM, resulting in endothelial and epithelial barrier disruption [31, 68].

The role of EVs derived from activated platelets on the pathogenesis of ARDS has also been demonstrated in ex-

perimental models of acute lung injury. Specifically, they dysregulate coagulation, enhance inflammation and contribute to alveolar-capillary membrane disruption [103, 136, 137]. Platelet-derived EVs activate monocyte and endothelial cells, on which they trigger the release of proinflammatory cytokines and increase their adhesiveness [149, 150]. Moreover, circulating platelet-derived EVs play an important role in vascular endothelial permeability; their levels have been considered promising biomarkers of endothelial dysfunction [151–153]. Indeed, they can transfer IL-1β to endothelial cells, augmenting vascular permeability via activation of the NLR family pyrin domain containing-3 (NLRP3)-inflammasome pathway [151–154]. They also can induce apoptosis in endothelial cells via miR-142-3p transfer [151–153, 155]. Elevated levels of TF have been found in circulating platelet-derived EVs in experimental models of acute lung injury and ARDS patients [156–158]. In general, platelet-derived EVs have been proposed to act as relevant clotting initiation agents, contributing to the severity of ARDS.

Finally, the release of lung-derived EVs into the systemic circulation following lung injury might spread the damage to distant organs. New knowledge of the implication of the EVs in mediating intercellular communication between structural—endothelial and epithelial cells—and immune cells during ARDS offers an extraordinary opportunity to understand specific pathological mechanisms fully and develop novel therapeutic strategies.

8. Multiorgan-lung interaction in ARDS

In ARDS, the exacerbated lung inflammatory response and the dysregulation of immune defense along with hypoxemia and coagulopathy alter other distant organs [54, 159–161]. At ARDS onset, 80 and 90% of the patients have at least one dysfunctional nonpulmonary organ system. The most prevalent is cardiovascular (73%), followed by hematologic (46%), renal (20%), and hepatic (19%) dysfunction. Nonpulmonary organ dysfunction is significantly greater in severe ARDS (reaching 90%) compared with mild and moderate ARDS. The number of the associated dysfunctional organs also increases with ARDS severity. On the other hand, patients with prior nonpulmonary organ dysfunction are at higher risk of developing ARDS, with worse evolution and increased mortality [162]. Therefore, it is becoming more apparent that the communication between the lung and other organs is a crucial determinant for the development and resolution of ARDS, leading toward an integrative approach in the management of critical patients.

8.1 Liver-lung interaction

The liver has multiple functions, such as the clearance of pathogens and their products and cellular debris, the metabolism of toxins and drugs, the synthesis of proteins, and the modulation of systemic inflammatory response and host defense [163]. Critical patients with previous cirrhosis and other chronic liver diseases have a higher risk of developing ARDS and worse clinical outcomes than patients with no liver diseases [164, 165]. On the other hand, hepatic dysfunction during the first 48-h period of moderate-to-severe ARDS is strongly associated with a worse outcome. It has been shown that early liver dysfunction and not kidney dysfunction is independently associated with death in ARDS patients ventilated according to a protective ventilation strategy [166]. Therefore, the bidirectional liver-lung communication seems to play a significant role in the development, progression, and resolution of ARDS [167].

8.1.1 Reticuloendothelial system in the liver

The liver harbors resident macrophages, known as Kupffer cells, which account for approximately 85% of the tissue macrophages in the body. These macrophages are involved in the clearance of pathogens and their products through phagocytosis and secretion of some mediators [168]. The dysfunction of the reticuloendothelial system of the liver facilitates the release of pathogens and PAMPs to the circulatory system, reaching other organs, such as the lung, in which they activate pulmonary and systemic inflammatory responses [169]. The liver also protects the lung due to the inactivation and detoxification of some molecules from the systemic circulation, including pro-inflammatory cytokines, vasoactive mediators, and eicosanoids [163]. The defective clearance of these products by the liver can cause damage to the alveolar endothelial-capillary barrier, activate immune cells, and promote platelet aggregation in the lung, contributing to the development of diffuse alveolar damage [170, 171]. During liver injury, hepatic immune cells release proinflammatory cytokines (IL-1β, IL-6, TNF-α), PAF, and leukotrienes to the systemic circulation [172]. In several acute inflammatory diseases, such as sepsis, it has been shown that those inflammatory mediators released by the injured liver can activate alveolar macrophages and impair lung function [173, 174]. In addition, increased oxidative stress markers and cytokines, such as TNF-α and IL-1β, have been found in the lungs of rats with tetrachloride (CCl4)-induced cirrhosis. Gas exchange and the size of pulmonary vessels are also altered in experimental models of cirrhosis [175, 176].

8.1.2 Acute-phase proteins, bilirubin, and extracellular vesicles

During infection or tissue injury, the organism initiates a systemic response, known as the acute-phase response, to restore homeostasis. This response is mainly mediated by the liver and includes relevant changes in the levels of acute-phase proteins (APPs) in plasma [177]. APPs include many molecules involved in pathogen clearance, immune cell recruitment, or antioxidant processes. Interestingly, in the lung of patients with ARDS, the activation of local alveolar inflammation triggers the acute-phase response in the liver. Moreover, in patients with ARDS induced by pneumonia, the pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) released by pulmonary immune cells lead to the synthesis of APPs by the liver, mainly via NF-κB activation [178, 179]. These liver-derived APPs, which include reactive protein C, SAA (serum amyloid A), or SAP (serum amyloid P), activate alveolar macrophages and trigger more cytokine release (CXCL1, IL-6), which lead to an enhancement of the neutrophil recruitment and oxidative stress in the alveolar spaces, contributing to lung damage [180, 181]. In addition, elevated levels of bilirubin produced in liver

diseases reach the alveolar space and alter the surface tension properties of the alveolar surfactant [182]. Growing evidence demonstrates that hyperbilirubinemia may contribute to the development of ARDS via activation of apoptosis, oxidative stress, and inflammation in different cell types [183, 184]. On the other hand, circulating EVs are increased during lung injury and in liver diseases [157, 185]. The potential role of these circulating EVs in liver-lung communication remains unknown and is an exciting field for future investigation.

Altogether, these observations evidence that the crosstalk between liver and lung seems to have a relevant role in the pathogenesis of ARDS.

8.2 Brain-lung interaction

The brain-lung interactions have also been reported in critically ill patients in both directions. It is well known that patients with brain injury can develop ARDS. In contrast, patients with ARDS frequently associate some neurocognitive deficiencies such as alterations in language, memory, and/or disorientation that can even persist a long time after discharge [54, 186, 187].

The neurological damages after lung injury remain unclear but may include the combination of hypoxemia, the effect of an activated systemic inflammatory response, and the circulatory changes caused by mechanical ventilation, including the effects of the positive end-expiratory pressure on cerebral microcirculation and intracranial pressure. The brain is an organ extremely sensitive to oxygen deprivation; thus, the hypoxemia resulting from ARDS seems to be a contributing but not the unique factor to brain dysfunction [187]. A recent systemic review has found an association between mechanical ventilation and acute cognitive impairment, describing greater neuroinflammation and lower cognitive scores in subjects with long-term mechanical ventilation [188].

In an experimental model of acute lung injury in pigs, Fries *et al.* [189] demonstrated elevated levels of the proinflammatory protein S-100B in serum and significant neuronal damage in the Cornu Ammonis, a subregion of the hippocampus that is especially vulnerable to a variety of pathologic conditions, such as ischemia, inflammation, and hypoxia. This hippocampal damage could explain the cognitive impairment associated with lung injury in patients.

A growing body of evidence indicates that the blood-brain barrier (BBB) permeability can be altered during systemic inflammation and/or infection because of the effect of circulating proinflammatory mediators (*i.e.*, IL-6, IL-1β, or TNF-α). These mediators activate cerebral endothelial cells, alter tight junction proteins and promote leukocyte transendothelial migration through the BBB, enhancing the local brain inflammatory responses. In this line, it has been shown that massive recruitment of monocytes into the brain initiates a complex neuroinflammatory response driving microglia polarization towards the M1 phenotype, which aggravates the cerebral inflammatory state, increases the BBB permeability, and activates different types of cell death by mechanisms involving the release of MMP9 and proinflammatory cytokine [190, 191].

The autonomic nervous system also plays an important role in the neuroimmune crosstalk between the brain and lung. The cholinergic pathway exerts an antiinflammatory effect that controls the systemic inflammatory response. In an experimental study of acute lung injury, Dos Santos *et al.* [192] showed that while vagus nerve inhibition enhances ALI, stimulation of the antiinflammatory cholinergic reflex exerts a protective effect in the lung.

Brain-lung interactions have received little attention in the literature, but a growing body of evidence suggests that both the lungs and brain establish a relevant cross-talk that modulates local and systemic inflammatory responses through common mediators.

8.3 Kidney-lung interaction

Acute kidney injury is also a life-threatening condition commonly presented in critically ill patients with systemic inflammatory response syndrome (SIRS), septic shock, or multiorgan dysfunction [193, 194]. Hemodynamic alterations induced by mechanical ventilation alter kidney perfusion and function by reducing the cardiac output, which leads to a redistribution of the renal blood flow with a reduction of the glomerular filtration rate and free water clearance [195, 196]. Mechanical ventilation also stimulates renin-angiotensin and sympathetic pathways, resulting in suppression of the atrial natriuretic peptide release. These changes lead to renal blood flow reduction and fluid retention [197, 198]. In addition, some preclinical studies suggest an essential role of several inflammatory mediators secondary to ventilator-induced lung injury (VILI) in developing acute kidney injury (known as ventilator-induced kidney injury). In experimental models of VILI, there is an increase of nitric oxide synthase (NOS) in both lung and kidney and of VEGF in serum along with systemic microvascular leak [199]. NOS enhances vascular permeability upon VEGF-ERK1/2 activation [200]. Increased levels of IL-6 and VEGF in the kidney have been shown in an experimental model of acid-induced lung injury in animals ventilated with high tidal volume (17 mL/kg) [201]. Apoptosis is also induced in kidney epithelial cells in animals with VILI. In ARDS patients, there is a correlation between elevated proapoptotic soluble Fas ligand and creatinine levels in the serum of ARDS patients [202].

In addition, hypoxemia has also been reported to alter kidney function, reducing renal blood flow by activating vasoactive factors such as angiotensin II, endothelin, and a decrease in nitric oxide that result in elevated renal vascular resistance [203, 204]. Moreover, in vitro models have demonstrated that low oxygen (O_2) and high carbon dioxide (CO_2) induced apoptosis in renal tubular cells [205].

On the other hand, detrimental effects of acute kidney injury on the lung have also been observed. In this line, acute kidney injury induced in animals results in a downregulation of epithelial sodium channel (eNaC), Na^+/K^+-ATPase, and aquaporin-5 in the lungs [206]. These proteins play relevant roles in fluid clearance and permeability of the alveolar epithelium; thus, dysregulation of these processes may lead to ARDS development. Acute kidney injury also elevates proinflammatory cytokines (IL-1β, IL-6, and IL-12) in serum leading to a secondary ALI characterized by pulmonary vascular congestion and neutrophil infiltration [207]. Another preclinical study in

mice shows that acute kidney injury is followed 4 h later by neutrophil infiltration, increased myeloperoxidase activation, and high levels of the neutrophil chemokines KC (keratinocyte chemoattractant) and MIP-2 along with capillary leak in the lung [208].

Altogether, kidneys could become damaged by mediators of inflammation or immuno-mediated factors related to ARDS, including the ventilator-related systemic and renal circulatory changes. On the contrary, it could be the renal disease determining consecutive pulmonary damage in critically ill patients.

9. Summary and conclusions

In summary, activation of PAMP and DAMP-mediated cell signals, dysregulated inflammatory response with pulmonary leukocyte infiltration, a procoagulant state, and the activation of cell death processes result in the disruption of the alveolar-capillary membrane and consequently in the protein-riched edema formation, in which weaknesses of the TJ complexes and alterations of the ECM in the alveolar epithelium play a key role. Inflammation and activated endothelial cells trigger coagulation cascades and platelet activation and aggregation. Activated platelets directly interact with neutrophils, facilitating their extravasation and recruitment into the lung and enhancing the systemic inflammatory responses. All these events generate a procoagulant state with the formation of fibrin in the airspaces and thrombosis in the microvasculature that aggravate alveolar injury and gas exchange. The crosstalk between alveolar epithelial cells, immune cells, platelets, and endothelial cells is mediated at least in part by EVs, which also mediate interorgan communication. Interaction of the lung with other organs has been revealed as an essential determinant in the development and resolution of ARDS.

Altogether, the pathophysiology of ARDS comprises many interconnected mechanisms responsible for modulating the onset and progression of lung injury. A complete understanding of the cross-talk between the different types of cells involved and the interaction of the lung with other organs will improve our knowledge of the physiopathogenesis of ARDS and offer an excellent opportunity to discover new biomarkers and novel therapeutic strategies in this and other clinical conditions.

AUTHOR CONTRIBUTIONS

PGR—conception and design, collection and assembly of information, manuscript writing, RH—conception and design, collection and assembly of information, manuscript writing, GS—collection and assembly of data, JAL—manuscript revision and approval of the final version of the manuscript. All authors contributed to the article and approved the submitted version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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