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The Basic Science and Molecular Mechanisms of Lung Injury and Acute Respiratory Distress Syndrome

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Introduction

Acute respiratory distress syndrome (ARDS) is a pathophysiologic state of inflammatory response to lung injury, which encompasses a heterogeneous group of direct and indirect causes, but with similar terminal pathophysiologic characteristics: vascular endothelial and alveolar epithelial cell damage, production of inflammatory mediators, and accumulation of inflammatory cells, mainly neutrophils, in the lung (1, 2). The structural damage is translated clinically into a syndrome of acute respiratory failure that debuts with dyspnea, progressive arterial hypoxemia secondary to severely impaired gas exchange, pulmonary edema, intrapulmonary hemorrhage, and marked increase in ventilatory work (3–7).

Thomas L. Petty and colleagues first described ARDS in 1967 in a heterogeneous group of patients and demonstrated the beneficial effect of PEEP to treat of patients with acute respiratory failure (8). The definition, pathophysiology, and treatment of ARDS, however, has evolved constantly throughout. Therefore, a historical comparison of patients within the context of ARDS is difficult and may become imprecise (9). The current incidence of this disease is estimated as approximately 200,000 patients annually in the United States with mortality rates ranging from 25 to 60% (10, 11). Yet, the data are not homogenous for all cohorts studied; for example African American and Hispanic patients have a higher mortality in ARDS than Caucasians and the difference can not be solely explained based on socio-economic status and access to healthcare (12–14). Thus, beyond population statistics, there is a need for molecular and biochemical pathway tools to provide better individualized diagnostics and therapies in the care for ARDS.

ARDS is defined according to the Berlin Definition consensus as an acute inflammatory response present in patients within 1 week of an insult, with bilateral pulmonary infiltrates, non-cardiogenic pulmonary edema, and arterial hypoxemia, using the arterial oxygen to inhaled oxygen ratio as *mild* (PaO_2/FiO_2 = 200 to 300), *moderate* (PaO_2/FiO_2 = 100 to 200),

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and *severe* (PaO_2/FiO_2 = 200 to 300), with PEEP ≥ 5 cm H_2O (15). The arterial hypoxemia is secondary to decreased blood gas exchange due to accumulation of edema and subsequent alveolar damage (16). In parallel, carbon dioxide elimination is also impaired, leading to higher respiratory rate, minute ventilation, and work of breathing.

Better survival rates due to improved supportive treatment with lung-protective ventilation, improved sepsis survival, and conservative fluid therapy are examples of physiologically based rational care based (9). However, we have no specific pharmacological therapy for ARDS approved to date (17, 18). We know that most patients who succumb to this syndrome do not die of hypoxemia or frank pulmonary failure, rather from multi-system organ failure that is likely mediated by the inflammatory mediators at play in this disease. Therefore, understanding these mediators and pathways is paramount to further development and hope for a pharmacologic treatment in the future.

In ARDS, an initial insult triggers massive liberation of inflammatory mediators, including *alarmins*, *complement activation products*, *cytokines*, *chemokines*, *proteases*, and *oxidants* (19–22). While sepsis and aspiration are frequent reasons for initiating ARDS, other etiologies are also observed (Table 1). Recent advances in the understanding of the molecular mechanisms responsible for the development of ARDS involving lung and systemic inflammation and tissue repair have opened a door to the development and improvement of new management strategies designed to increase survival. However, considerable work is needed to translate the basic research knowledge on lung injury to clinical practice.

To understand the molecular alterations observed during lung injury, one needs to know the normal molecular dynamic of the lung, which is a highly specialized organ with main functions in gas exchange, blood circulation regulation, and defense (23–26). Lungs are a primordial example of innate and adaptive immunity collaboration of the human body (Figure 1). In this complex organ, no single mechanism can fully account for all the molecular complexities observed. In this chapter, we focus on the molecular, structural, and physiological bases that contribute to ARDS. We describe the proteins, peptides, and other molecules that are and could be used as biomarkers for disease severity and therapy in ARDS. Molecular mechanisms of lung injury will undoubtedly provide better insights into the operative and perioperative management of critically ill patients.

Acute Lung Injury in Mechanical Ventilation

An appropriate knowledge and analysis of mechanical ventilation (MV) is necessary for proper care of the ARDS patients (27). The objective of MV is to decrease the respiratory work, providing adequate gas exchange, while minimizing injury (28). However, since the first descriptions of the use of mechanical ventilation, ventilator-associated lung injury has been reported to either initiate lung injury or augment underlying lung injury, coining the term ventilator-induced lung injury (VILI) (29, 30).

The pressure to move air into the alveoli requires forces necessary to overcome the airway resistances, the gas acceleration resistance (*inertia*), and the elastic properties of the lung as

well as the chest wall. Clinically, the transpulmonary pressure, a measurement of the distending force applied to the lung to inflate the lung and distend the chest wall (*alveolar pressure minus pleural pressure*) is difficult to calculate, but can be estimated through measuring the esophageal pressures (31). The plateau pressure (a surrogate measure of alveolar pressure) can be easily obtained during mechanical ventilation by applying an inspiratory pause on the ventilator. Variables having an effect on the plateau pressure measurement include respiratory efforts and chest wall stiffness. The differences of transpulmonary pressure, as a consequence of imbalance between lung stress and strain (*barotrauma*), have been identified as main drivers of VILI (32). Other factors attributed include volutrauma (injury secondary to regional overdistention), atelectrauma (cyclic collapse or re-opening of airway units), and biotrauma (cell signaling and direct release of cell mediators induced by physical forces) (33). With a heterogeneous distribution of transpulmonary pressures, it is a challenge to achieve optimal airway distension to prevent VILI. While it is tempting to achieve an open lung strategy by applying higher levels of positive-end expiratory pressures (PEEP), thus preventing atelectasis, recent work suggests that such an approach also increases the risk for volutrauma (33). We will attempt to focus on the molecular mechanisms of injury that result from the mechanical transduction of physical stress on the alveoli, i.e, biotrauma.

In all these scenarios, alveolar-capillary barrier dysfunction results in increased endothelial and epithelial permeability, alteration of surfactant function, and inflammation propagating the injury further (34). In general, the pathogenesis of ARDS is divided into three phases that frequently overlap temporally and spatially: exudative, proliferative and resolution (35, 36). Further, VILI can change the trajectory of ARDS, acting as an independent risk factor for patient outcomes.

Initial insult

Predisposing conditions

Predisposing conditions within and outside of the lung, also called “intrinsic” and “extrinsic” factors, are implicated in ARDS development (37, 38). Intrinsic factors include genetic predispositions and anatomic malformations, and extrinsic factors include comorbidities and environmental triggers (Table 1). Recently, it has been identified that some genes contribute to both susceptibility as well as severity of the disease (Figure 2) (39–45). Others genes associated with cell regulation, cell growth, and apoptosis have also been related to the pathogenesis of ARDS. Those genes include p53, p16INK4a, p15INK4b, WT1 (Wilms’ Tumor 1), and ATM (ataxia telangiectasia mutant) (46–48). P53 may be particularly important in ARDS, since overexpression of p53, at protein and transcription levels, occurs frequently in pulmonary fibrotic disorders. Poly(ADP-ribose) polymerase (PARP), a putative p53 regulating protein, is needed for the fibroplastic activity, since PARP deficient V79 fibroblasts are unable to induce p53 mRNA and are incapable of undergoing apoptosis (49). Independent mechanisms triggered via cell senescence, TGF-β and ROS (reactive oxygen species) have all been implicated in the mechanism of development of ARDS (50, 51).

As described previously, extrinsic factors can trigger lung injury (Table 1), including chemical, biologic, and physical agents (52). Chemical agents include occupational particles

(asbestos), and dust; biologic agents such as virus, bacteria, fungi and parasites; and finally, physical agents include inhalation of hot and harmful gases (53).

In addition to the complexity observed in ARDS, other previous co-morbidities can aggravate ARDS and worsen the prognosis. Moreover, patients with ARDS are commonly treated with MV; therefore the risk of VILI is inherently present. Thus, there is an interplay between the lungs suffering from ARDS and mechanical ventilation supporting the system with minimal injury.

Immune mediated Lung Injury

Early in ARDS, after an initial injury that triggers the liberation of alarmins, the exudative phase sets in. This early response is then amplified by the NLRP3 (NLR Family Pyrin Domain Containing 3) inflammasome, which is heavily regulated by Toll-like receptors (TLRs). NLRP3 is a major intracellular multiprotein inflammatory pathway of the innate immune system leading to IL-1β, IL-18, and caspase-1 activation and apoptosis as well as pyroptosis (54). Subsequently, elevated levels of both IL-1β and IL-18 are associated with poor long-term survival in ARDS (55, 56). The NLRP3 inflammasome triggers or alarmins are divided in endogenous factors (DAMPS –Damage Associated Molecular Patterns, ATP, uric acid crystals) or exogenous factors (bacterial hemolysins, pneumolysin, etc.), and are regulated by TLRs and NF-κB (57, 58). The regulatory effect of TLRs is established through the TLR-4 receptor signaling, which shows remarkable similarity to IL-1β signaling (57). This leads to subsequent cell activation of monocytes and macrophages, establishing a cascade of inflammatory cell recruitment and later release of active mediators. Polymorphonuclear neutrophils (PMN) and alveolar epithelial cells mediate this initial phase of intrapulmonary inflammation. This initial response also leads to a potent release of interleukin (IL)-12 and IL-23, promoting strong proinflammatory Th1 immune responses (59, 60). In addition, they trigger the release of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and other proinflammatory cytokines (e.g., TNF-α, IL-6) leading to apoptosis and necrosis. The apoptotic pathway most studied in ARDS, the Fas/FasL system, is mediated by the TNF-α death membrane receptor Fas (CD95) and its natural ligand (FasL) (61). Increased FasL concentrations in BAL from ARDS patients are also associated with an increase in mortality (46).

Lung injury mediated by mechanical forces—Ventilator-induced ARDS is the result of a complex interplay among diverse physical forces on lung anatomy during mechanical ventilation (62–65). Even the pattern and degree of stretch are relevant in determining cellular and molecular response, or biotrauma (66, 67). In addition to mechanical injury, stretch-induced trauma leads to the appearance of inflammatory mediators such as extracellular histones (68). Extracellular histones are proinflammatory mediators; they directly activate the NLRP3 inflammasome, resulting in neutrophil recruitment (69, 70). This process of conversion of mechanical stimuli into a biochemical signal (i.e. biotrauma) is called *mechanotransduction*. Cells act as mechanosensors after stimulation for physical forces, motion, osmotic forces, shear stress, and interactions between cells and/or cell matrix (71). The mechanical stretch induced by mechanical ventilation regulates ionic channels, including Na-K- ATPase and Ca^{2+} activity, factors that may play important roles in

pulmonary edema development and clearance (72). Ca^{2+} also induces *fos* gene expression, as shown in pre-clinical models, propagating the lung injury. Interestingly, systemic inflammation increases the sensitivity of the lung epithelium to injury (73, 74). Additionally, mechanical injury induces translocation of NF-κB into the nucleus unleashing several proinflammatory cytokines and chemokines from macrophages upon mechanical stretch, such as IL-6, IL-8, IL-1β, and TNF-α, and this could be activated independent of TLR4 pathways (75). Follow-up human studies have demonstrated that patients who are ventilated with lower tidal volumes and lower airway pressures had a reduction in interleukin IL-8, −6, soluble TNF receptor 1, and neutrophils (76).

Moreover, mechanical forces can induce direct expression of immediate early response genes, such as c-*fos*, c-*jun*, c-*myc*, IL-1β, and Egr-1 (75). An initial release of pro-inflammatory cytokines and chemokines has long term effects, such as pulmonary fibrosis and thrombosis via platelet-derived growth factor-B, tissue plasminogen activator, intracellular adhesion molecule-1 (ICAM-1), and TGF-β in lung fibrosis (77, 78). Mechanical forces also regulate the production of ROS through the activity of nitric oxide synthase and cyclooxygenase-2 leading to endothelial and epithelial damage (79).

Transfusion-Related Acute Lung Injury—Transfusion-related ARDS is an uncommon complication during or shortly after transfusion. In recent years, the alterations of several inflammatory markers have been described in this immune mediated injury. Multiple factors, such as female donors, neutrophil alloantigens, platelets activation, sepsis and ischemia-reperfusion injury, have been implicated in this process (80–82). Vigilance in keeping TRALI in the differential diagnosis as well as restrictive use of blood has led to a relative decrease in its incidence, yet TRALI continues to be an independent risk factor for mortality (83). More information on this type of lung injury is available elsewhere in this volume.

Anatomic basis, pathophysiologic and molecular mechanism—Conducting airways and alveoli are both derived from the endoderm-derived bulbs (84). The alveoli are covered by a simple squamous epithelium composed of two types of cells, pneumocytes type I and II. This epithelium is a tight barrier impermeable to proteins and solutes. The flat type I pneumocyte covers around 90% of the alveolar surface; they have abundance in lipid-rich lamellar bodies, and high expression of MUC1, ABCA3, and surfactant proteins (SP) that decrease the alveolar surface tension, along with other biologic functions (85). The more cuboidal type II pneumocytes cover the remaining extension, and they have the critical role of surfactant synthesis/regulation, and as progenitors for type I pneumocytes. Mature airways are lined by an impermeable cylindrical pseudostratified epithelium with abundant superficial cilias. The permeability barrier is maintained by inter-cellular junctional proteins including claudins (Cld), connexins (especially Cnx43), paranexins, adhesins, and occludins (86–88). Gap junctions rapidly exchange the stimulus-induced responses among ciliated cells. The number of ciliated and non-ciliated cells varies along the airways, and their number is strongly influenced by toxic and inflammatory processes. The epithelial cells are interspersed with secretory goblet cells that produce abundant mucins, fluids and electrolytes (Cl^- and HCO_3^-) together with the submucosal glands that produce mainly MUC5B and fluids. These mucins form a highly adhesive thin mucous aqueous subphase that creates a

direct host defense barrier able to disrupt bacterial aggregation, adhesion and internalization into the epithelial surface. Furthermore, epithelial cells secrete host defense molecules and proteases such as human β-defensins, lysozyme, lactoferrin, cathelicidin LL37, and surfactant proteins. The joint work between the aforementioned mechanisms create an escalator apparatus that is able to mobilize harmful chemical, physical, and microbiologic agents from the surface of the airways (89). The crucial engine of this apparatus is the coordinated directional movement of cilia regulated by paracrine signals, including purinergic signaling. They are composed by microtubules associated with dynein arms to form axonemes that are powered by ATP (90).

Both airway and alveoli epitheliums are anchored to the extracellular matrix (ECM) through a basal membrane. The ECM is composed of collagen and elastic fibers, surrounded by an amorphous substance rich in glycosaminoglicans such as hyaluronan. The space formed in the ECM is also known as interstitial space. The epithelial ciliated cells as well as the secretory goblet cells originate from epithelial stem cells that express α6β4 and are located in close proximity to the epithelial basal membrane. These epithelial stem cells play a critical role in airway regeneration after injury (91). Their differentiation is determined by the transcription factor SOX2 and requires SPDEF, a transcription factor that regulates genes encoding a network of molecules involved in mucus biosynthesis (92, 93). Such pluripotency will be important during the recovery phase in ARDS. In the interstitial space of the alveoli are macrophages with surfactant catabolism and the innate immune defense functions. Impairment of the surfactant regulatory effect of macrophages leads to acquired pulmonary alveolar proteinosis (Figure 3).

The pulmonary surfactant and alveolar liquid subphase keep the alveolus expanded. Pulmonary surfactant is composed mainly of lipids and limited amount of SPs (mainly SP-A and SP-D). Its main role is to reduce surface tension in the alveolus during the dynamic ventilation changes, but also actively participate in the opsonization and killing of pathogens, mediating in the regulation of macrophages, neutrophils and lymphocytes by pathogen-associated molecular patterns (PAMPs) (94–96). Additionally, the main surfactant lipids dipalmitoylphosphatidylcholine and phosphatidylglycerol have intrinsic antimicrobial activities. Type I pneumocytes act as alveolar mechanosensors, responding to the stretch of lung expansion by conveying surfactant-secreting calcium mediated signals to the type II pneumocytes.

Exudative Phase

Increased permeability and pulmonary edema: ARDS is characterized by an initial exudative phase, which presents with diffuse alveolar damage associated with severe accumulation of liquid forming pulmonary edema (97). This hydraulic imbalance governs together with the already described barometric alteration in the pulmonary microvasculature. A major microvascular pressure produces an enhanced filtration into the pulmonary interstitium. A higher conductance product of endothelial cell activation, mediated by P-selectin, also allows the high filtration and release of thromboxane A_2 observed in ARDS (98). Thromboxane A_2 activates endothelial thromboxane A_2 receptors and induces de novo expression of ICAM-1, triggering firm PMN adherence to endothelium via β_2-integrins (99).

The alterations of both barometric and hydraulic forces induce the release of inflammatory mediators and gene transcription. The concentrations of the liberated inflammatory mediators are intimately linked with the grade of severity of the injury. Two relevant mediators are IL-1α and IL-6, which activate neutrophils and monocytes, inducing the liberation of ROS with damage of the endothelium (100). Additionally, angiopoetin-2 (Ang-2) also regulates vascular permeability, promoting cell death and vascular regression (101). The production of neutrophil extracellular traps (NETs) also damage the lung endothelium contributing to the edema (102).

Endothelial injury: The microvascular damage induces hyperpermeability after the formation of gaps between endothelial cells mediated by myosin light-chain kinase (MLCK) phosphorylation and subsequent contraction. Endothelial wall integrity and maintenance of the epithelial/endothelial barrier requires epithelial (E-cadherin)- and vascular endothelial cadherin (VE- cadherin)-mediated adherence of the junction bonds (103, 104). A proinflammatory state with elevation in vascular endothelial growth factor, TNF-α, or histamine induces Src-mediated phosphorylation of VE-cadherin at Tyr685 (p-Y685), which leads to endothelial activation and higher permeability (105).

In ARDS, high intravascular hydrostatic pressure and endothelial cell activation lead to massive leak of plasma, including large proteins such as albumin. Subsequently, the intravascular-interstitium balance of proteins is altered, and a disruption of the oncotic pressure results in worsening of the pulmonary edema, restriction of the effective gas exchange and thus hypoxemia.

Parallel to the development of edema, the initial proinflamatory stimuli leads to the recruitment and accumulation of neutrophils in the pulmonary microcirculation, where they are activated, producing NETs and ROS with subsequent direct endothelial wall damage (106). Non-activated neutrophils perform endothelial cell adhesion rolling, chemotaxis, sequestration and activation in the lung interstitium due to the activity of IL-8, epithelial neutrophil-activating peptide (ENA-78), and β_1 and β_2 integrins (107). Integrins mediate cell adhesion by interaction with adhesion molecules (for example, intercellular adhesion molecule [ICAM]-1, ICAM-2, vascular cell adhesion molecule [VCAM]-1). During ARDS, neutrophils adhere to the endothelium in an integrin–dependent or in an integrin–independent mechanisms that are activated after highly antigenic or other mediators (99, 108).

Epithelial injury: As previously described epithelial cells or pneumocytes line the alveolar wall. They play critical roles including the functions of protective barrier, regulating surfactant production, and fluid homeostasis. In ARDS, alveolar epithelial cells undergo severe damage following insults of neutrophils, proinflammatory cytokines, hypoxia, and physical forces. All of these insults induce cell damage by autocrine or paracrine apoptotic mechanisms (109, 110). Mitochondrial-mediated apoptotic pathways also contribute to this increased apoptotic rates (110). In addition, the activation of the Fas/FasL pathway is important in mediating apoptosis in ARDS. Apoptosis is induced when membrane-bound or FasL binds to Fas-bearing cells.

In the airways multiple epithelial changes are observed during ARDS. Alterations in the number of ciliated cells, goblet cell metaplasia and excessive mucus production are all observed. The development of these changes are linked to inflammatory signaling via TLRs and transcription factors of the IRF and NF-κB families and cytokine signaling via the Jak kinase–STAT transcription factor pathway in respiratory epithelial cells. Airway Clara cells are altered during ARDS, which are normally devoted to the protection of the respiratory tract against toxic inhaled agents, the repair of damaged epithelium, xenobiotics detoxification, and the secretion of proteins with important biological activities. The Clara cell protein (CC16) is highly expressed after injury and possibly increasing the product by modulating the production and/or activity of phospholipase- A2, interferon-γ, and TNF-α.

Lung extracellular matrix alteration: The extracellular matrix (ECM) forms the region of the lung situated between the alveolar wall and the blood vessels; it is also known as lung interstitium. ECM is a complex and dynamic meshwork that regulates cellular and extracellular functions including development, nutrition, proliferation, repair, and migration. ECM is composed of protein fibers and amorphous substance. The protein fibers are mainly collagen and elastin, and the amorphous substance is composed of water, glycoproteins, and proteoglycans including hyaluronic acid. In ARDS, lung ECM undergoes significant remodeling because of physical damage as well as degradation of its components, including hyaluronan fragments (111–113). If the damage is not controlled, it can lead to irreversible structural changes as well as progressive inflammation with long-term sequelae, including lung fibrosis (114, 115). An adequate clearance of hyaluronan fragments is necessary to allow adequate healing, a process dependent on the hyaluronan receptor CD44 (113). Unquenched hyaluronan degradation products on the other hand can induce chemokines, cytokines, growth factors, signal transduction molecules, and adhesion molecules propagating inflammation and injury (116).

The family of zinc-dependent enzymes, matrix metalloproteinases (MMPs), are responsible for ECM remodeling and these enzymes are produced by a variety of cell types, including macrophages, monocytes, and PMNs (117, 118). MMPs are known to exert a myriad of regulatory actions critical in tissue repair and remodeling, including epithelial cell migration, proliferation, differentiation, and apoptosis, as well as release of latent or bound growth factors from the ECM. In ARDS, MMP-2 (gelatinase A), MMP-8 (collagenase 2), and MMP-9 (gelatinase B), are extensively studied and their concentrations correlate with clinical severity (119, 120). In addition to degrading the epithelial and endothelial basal membrane allowing migration of inflammatory cells, MMPs modulate inflammation by either activating or inactivating cytokines and chemokines (121, 122).

Neutrophil-Mediated Injury: Excessive recruitment and activation of neutrophils with subsequent recruitment of monocytic cells is observed in early stages of ARDS. This leads to release of toxic enzymes, damage of alveolar epithelium, vascular leakage, pulmonary edema, and hypoxemia. Phagocytic cells, both neutrophils and macrophages, respond to several potent chemoattractants expressed during lung injury, including IL-17, macrophage inflammatory protein-2 (MIP-2), CCL3, and CXCL2. These phagocytic cells are terminally differentiated effector cells with primary roles in innate immunity. They are able to perform

phagocytosis of pathogens, production of reactive oxygen intermediates and toxic enzymes such as elastase, and formation of neutrophil extracellular traps (NETs) (99, 123).

NETs have been recently described as an innate immune mechanism, which increases the local capture of pathogens by the DNA. When neutrophils are activated, they emit their DNA fibers, which carry nuclear and cytoplasmic proteins, including histones, elastase, myeloperoxidase (MPO), pentraxin, cytokines, MMPs, and bactericidal peptides (124). The DNA fibers rich in proteolytic and pro-inflammatory molecules are interwoven to create web-like structures able to capture and destroy pathogens. While effective, this massive response may lead to tissue damage because its effect is non-specific, injuring the endothelium (*vasculitis*), alveoli, terminal bronchioles, and extracellular fibers allowing the formation of abscesses and damage of the alveolar–capillary barrier (102). Interestingly, bacteria such as Streptococcus pneumoniae and Staphylococcus aureus can produce endonucleases able to digest NETs (125). ROS and MPO together with neutrophil elastase are known to mediate NETs induction (126).

Chemokines, cytokines, and lipid signaling molecules-mediated inflammation and injury: The role of cytokines, cytokine binding proteins, and growth factors in regulating ARDS pathology has been extensively studied. The ARDS inflammatory cascade involves release of these mediators, where alveolar macrophages and PMNs are considered the primary source of these molecules, but they are also produced by type II pneumocytes (127, 128). Yet, both proinflammatory cytokines (IL-1 −6, −8, −18, TNF-α, and TGF-β) and anti-inflammatory cytokines (IL-10, −13) are altered in ARDS, making it a balancing act (129). Other mediators implicated in lung injury include omega-3 fatty acid derived lipid mediators released from cell injury during the early phases of ARDS (130).

Oxidant-Mediated Injury: Oxidative-mediated mediators are implicated in the development of lung injury. Toxic reactive oxygen species (ROS) are generated from normal cellular respiration and aerobic metabolism, and increased significantly under cellular stress and damage. In injury, several free radicals, such as hydrogen peroxide (H_2O_2), superoxide anion (O_2^-) and the hydroxyl radical (HO^-), and reactive nitrogen species (RNS), produce deleterious effects (131, 132). These oxidative mediators are regulated at both cellular and mitochondrial levels.

The most frequent pathophysiologic basis of noninfectious ARDS is hyperoxia-induced injury secondary to free oxygen radicals (133). The hyperoxia effect killing type II pneumocytes appears to be mediated by p53 as well as p21 dependent mechanisms, which also play a role in long-term fibrosis (134–136). TLRs contribute to increased inflammation during hyperoxia in the absence of infection via NF-κB activation (137, 138). Tyrosine kinase (TK), protein kinase C (PKC), and mitogen activated protein kinase (MAPK) signaling cascades also activate NF-κB pathways.

The second mechanism implicates the release of ROS, especially O_2^- and H_2O_2, upon activation of inflammatory cells (139). In endotoxin mediated ARDS, radical oxygen species are formed by inducible cyclo-oxygenase-2 and inducible nitric oxide synthase (iNOS) in alveolar macrophages (140). The activation of these enzymes also causes increased

pulmonary microvascular permeability especially in burn and smoke inhalation mediated injuries, and activation of response genes (*c-fos* and *c-jun*), and pro-apoptotic FAS and FAS-ligand in alveolar macrophages and alveolar epithelial cells suggests that ROS play a critical role in ARDS mediated apoptosis and cellular injury (141).

A third mechanism is the liberation of ROS from the mitochondria (142). Mitochondrial superoxide dismutase converts the superoxide to H_2O_2, which diffuses out of the mitochondria to activate cytosolic targets such as Weibel-Palade bodies, causing endothelial expression of P-selectin, and activating the NF-κB pathway. The mitochondrial participation depends on Ca^{2+}-induced activation of mitochondrial electron transport.

Other mechanisms include restitution by hydrogen donation, nucleotide excision, and recombination, such as nicotinamide adenine dehydrogenase (NADPH) oxidase, xanthine/xanthine oxidase, and/or phospholipase C pathways, also activated during ROS production in lung injury (143).

Counter-regulatory mediators including both non-enzymatic and enzymatic antioxidant defenses are activated to protect the lung tissue from the deleterious effects of ROS. Non-enzymatic defenses include vitamins, bilirubin, sulfhydryl-containing glutathione, albumin, ceruloplasmin, hemosiderin and transferrin/lactoferrin. In addition, enzymatic antioxidants counter balance superoxide dismutase. Such enzymes are Superoxide Dismutase (SOD), Myeloperoxidase (MPO), catalase and glutathione-S-transferases, and peroxidases. These enzymes also regulate NETs, suggesting a complex balance between the protective and destructive effects of ROS in lung injury (144).

Coagulation and fibrinolysis: ARDS is characterized by alterations in both systemic and intra-alveolar coagulation and fibrinolysis. Blood coagulation pathways are involved in ARDS. The inflammatory endothelial damage has an effect inducing the formation of thrombin creating a hypercoagulable state (145). In addition, inflammation activates the endothelium and reduces blood flow with subsequent higher propensity for thrombosis. Thus, the formation of thrombi and vasculopathy is a common event in ARDS.

Increased levels of coagulation factor III (tissue factor) and plasminogen activator inhibitor type 1 mediated by IL-1 and −6 have been reported during ARDS (145, 146). These two mediators lead to the activation of the extrinsic pathway of coagulation and inhibition of fibrinolysis, respectively. They also mediate the degradation of fibrin and induce platelet activation. Additionally, inflammatory mediators induce plasma prekallikrein (*KLKB1*) production, leading to a potent vascular permeability stimulus (147).

Thrombosis and fibrin deposition is a beneficial counter regulatory mechanism able to quickly repair the disrupted vascular and alveolar wall. This effect is mediated by von Willebrand Factor (vWF). However, massive fibrin deposition and thrombosis can lead to activation of neutrophils and fibroblasts, endothelial injury, loss of surfactant activity favoring alveolar collapse, and impaired alveolar fluid clearance.

Fibroproliferative phase—When a persistent or massive injury occurs and counter regulatory mechanisms cannot resolve the damage, persistent inflammation results in a

fibroproliferative response. Accumulation of macrophages, fibrocytes, fibroblasts, and myofibroblasts in the alveolar and interstitial compartment contribute to excessive deposition of ECM (50). Macrophages contribute to the fibroproliferative phase in ARDS, producing numerous proinflammatory mediators (IL-1, - 4, and −13) and growth factors (transforming growth factor [TGF]-α, TNF- α, platelet derived growth factor [PDGF], fibroblast growth factor [FGF], and insulin-like growth factor [IGF]-I) (148).

While alveolar wall repair is mediated by keratinocyte growth factor (KGF), hepatocyte growth factor (HGF), FGF, and TGF- α, endothelial wall repair is mediated by VEGF and HIF-1α (149, 150). Proliferating cells are regulated and eliminated through apoptosis, resolving the massive cell infiltrate and pneumocyte type II cell hyperplasia; fibrosis develops when these counter regulatory mechanisms are arrested or fail.

TGF-β production is the main mediator implicated in lung fibrosis development. Other soluble factors such as endothelin and thrombin may mediate similar effects, although their relative roles in fibrotic diseases of the lung are unclear (51, 151). Multiple cell types synthesize TGF- β such as alveolar macrophages, lymphocytes, fibroblasts, and pneumocytes. This cytokine mediates its activity through p53 and cyclin E encoding for connective tissue matrix accumulation, pulmonary mesenchyme cell growth and chemotaxis, and arrest of counter fibrotic mechanisms (152).

Leukotrienes (leukotriene D4) and prostaglandins (in particular PGE2), oppose fibrotic changes in ARDS. Potential antifibrotic mechanisms of action of PGE2 include inhibition of fibroblast proliferation, migration, contractility, and myofibroblast differentiation (153).

Resolution phase—Despite the severe clinical and molecular manifestations of ARDS, the majority of patients survive. This illustrates clearly that repair mechanisms can reestablish normal or near-normal endothelial and epithelial barriers and normalize the structure and function of the injured alveoli. An effective lung repair in ARDS requires correction of both micro-vascular hyper-permeability and edema. The alveolo-capillary barrier repair depends on effective and rapid adherents junctions being re-established. A rapid re-absorption and fluid clearance from inside the alveoli is also required. Several catecholamine-independent pathways, including glucocorticoids and thyroid hormone, increase the rate of alveolar fluid clearance (154, 155). Na, K-ATPase pumps and the CFTR (cystic fibrosis transmembrane regulator) play a key role regulating the alveolar fluid transport (156, 157). The first step toward resolution of ARDS is to remove the alveolar edema fluid to the lung interstitium, where net clearance can occur through lung lymphatics, the pulmonary microcirculation and even bulk flow into the pleural space. Removal of alveolar edema fluid from the air spaces requires vector transport of sodium and chloride across the apical and basolateral membranes of alveolar epithelial type I and II cells, which creates an osmotic gradient for the reabsorption of water. Thus, sodium is actively absorbed across the apical surface of alveolar epithelial type I and II cells, predominantly by the epithelial sodium channel; the sodium is then extruded from the cell by the Na/K-ATPase pumps on the basolateral membrane. Chloride is transported by the transcellular and perhaps the paracellular route, although the molecular pathways are not completely understood.

Conclusion—ARDS continues to be a clinical challenge, yet there have been significant improvements in the acute mortality in the last 20 years. Lung protective approaches to mechanical ventilation (low Tv and appropriate use of PEEP) along with a multi-disciplinary approach to the patient have led to this overall improvement, presumably through less iatrogenic lung injury (VILI). However, we are still faced with the long-term challenges, including the reality that most patients dying from ARDS perish from unmitigated multisystem organ dysfunction rather than the direct lung injury itself. Therefore, as we continue to improve our understanding of the inflammatory pathways and mediators, we hope to develop further treatments and strategies to improve the complications and management of this syndrome to further improve the survival (158).

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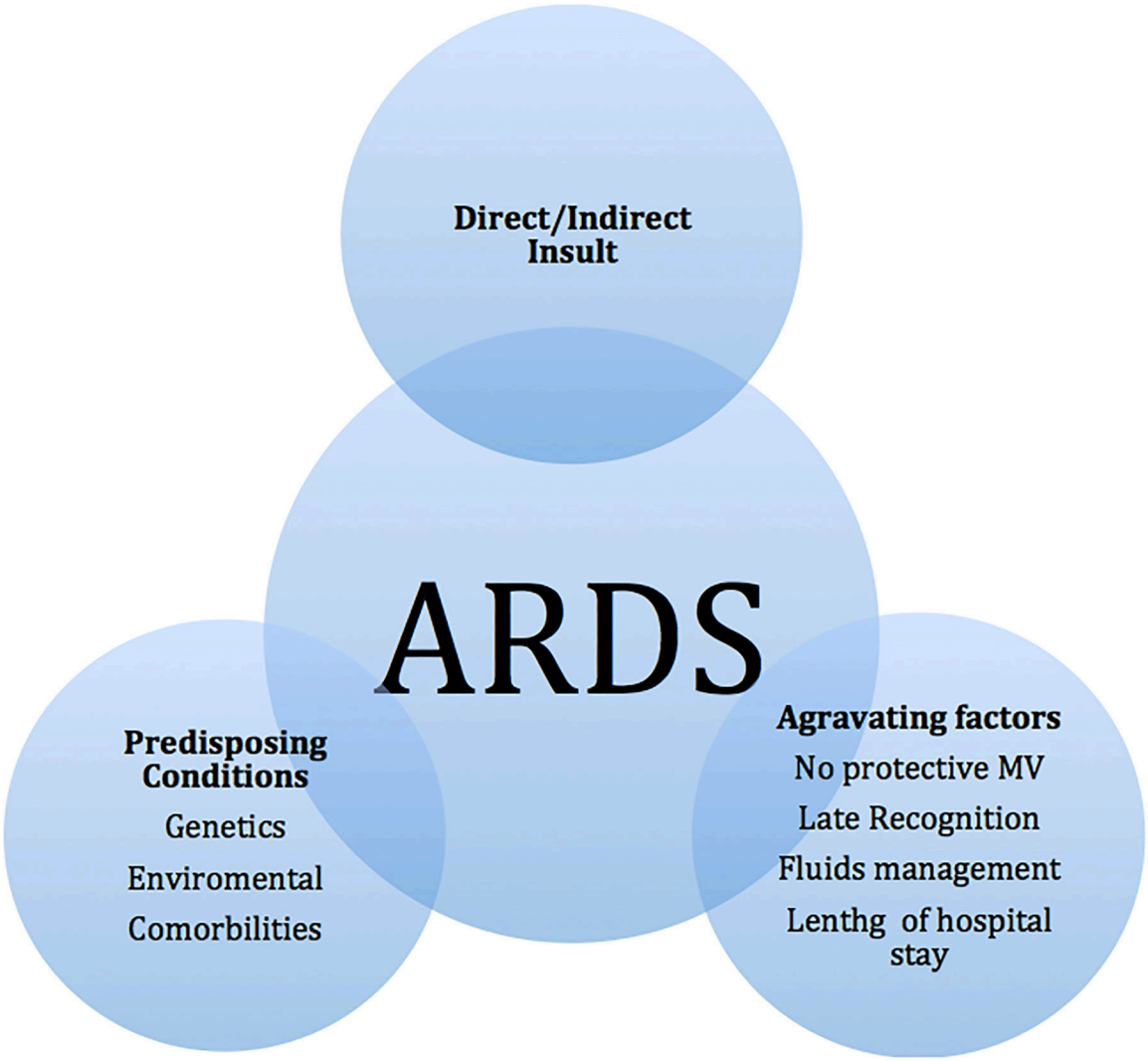

Figure 1.
Associated factors to the development of ARDS

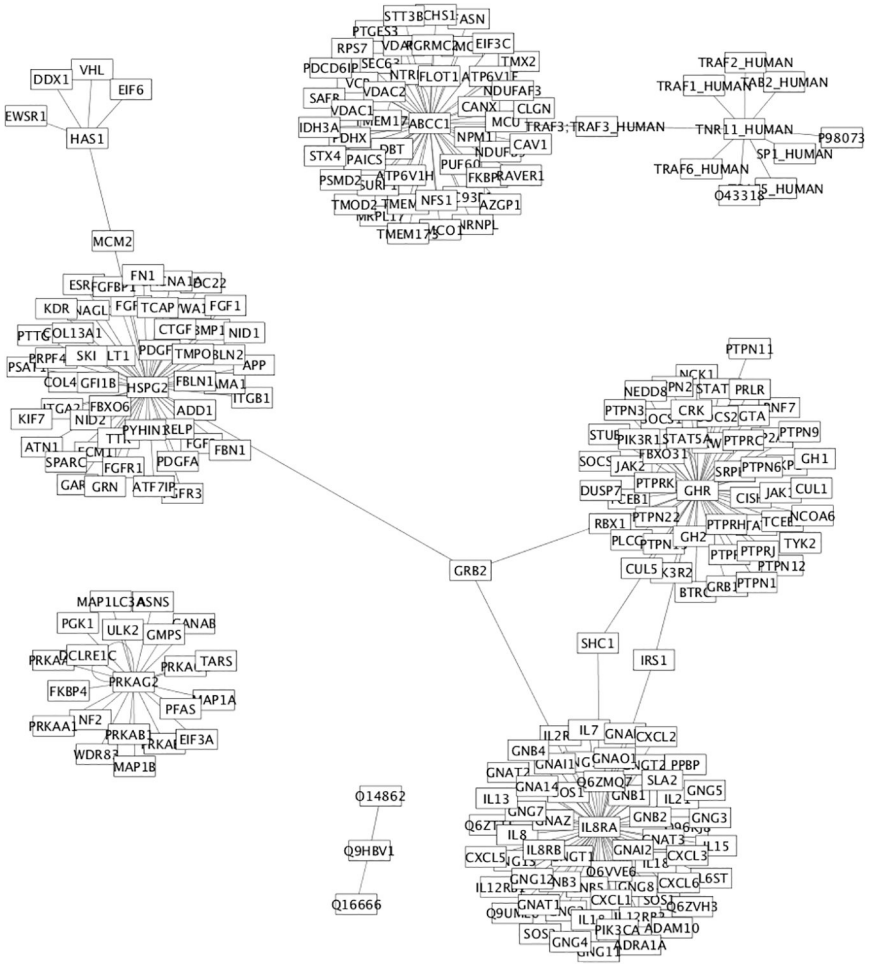

Figure 2.
Genes implicated in direct ARDS

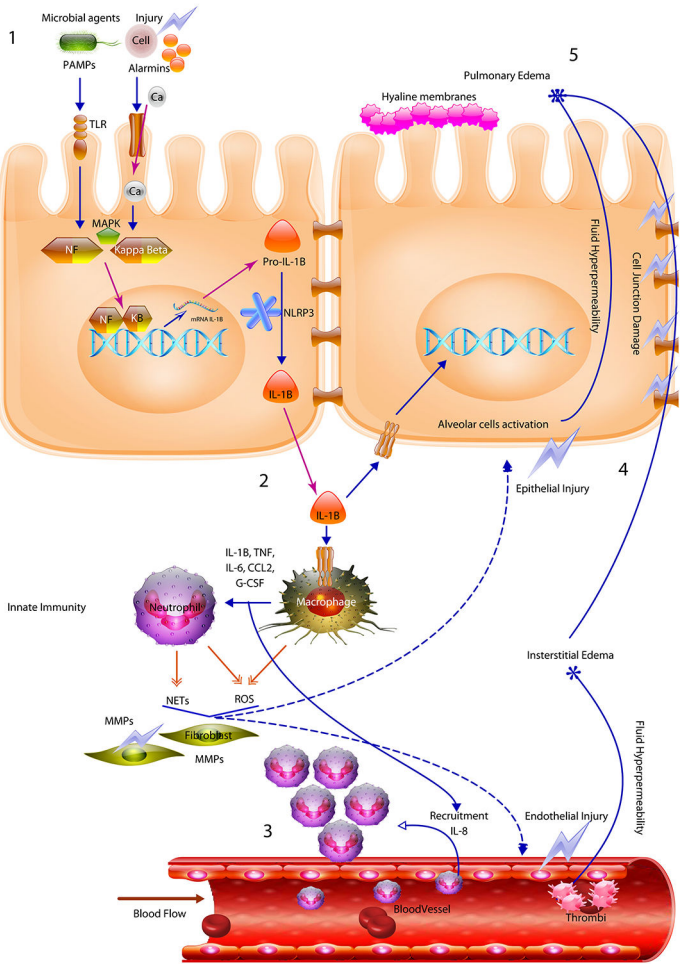

Figure 3.

Pathogenesis of the ARDS is triggered after an initial injury that interacts through alarmin receptors and toll like receptors activating nuclear transcription factors including NF-Kappa-beta. Then a powerful acute immune response triggered mainly by IL-1B causes macrophage/neutrophil activation and recruitment. The cell mediated immune response produces tissue damage mediated by NOS and NETs allowing the development of edema and epithelial damage.

Table 1.

Causes and predisposing factors for ARDS

Factor		**Association**
Individual	Age	Risk
	Male gender	Risk
Genetic	Genes	Risk
	Polymorphisms	Risk and severity
Anatomic	Malformations	Risk
	Structural defects	Risk
Comorbidities	Aspiration of gastric contents	Causative
	Acute pancreatitis	Risk
	Chronic alcohol abuse	Risk and severity
	Coronary artery disease	Risk and severity
	Diabetes	Risk and severity
	Embolism (air, fat, amniotic fluid)	Causative
	History of smoking	Risk and severity
	Ischemia-reperfusion injury	Causative
	Multiple transfusions of blood products	Risk
	Pulmonary contusion	Causative
	Pulmonary infection	Causative
	Sepsis	Risk
	Severe trauma with shock	Risk
	Vasculitis	Causative
Environmental	Burn (massive)	Risk
	Inhalational injury (smoke, noxious gases)	Causative
	Medications (opioids, salicylates, amiodarone, tocolytics, chemotherapy)	Risk
	Near drowning	Causative
	Thoracic irradiation	Causative