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REVIEW

Lung remodeling associated with recovery from acute lung injury

Sean E. Gill[1,2] · **Cory M. Yamashita**[1,2] · **Ruud A. W. Veldhuizen**[1,2]

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Abstract Acute respiratory distress syndrome (ARDS) is a disease with a variety of causes and is defined by severe hypoxemia. Whereas ARDS carries a mortality of approximately 30 %, patients that survive may ultimately regain near normal pulmonary physiology. The critical pathophysiological processes in ARDS are alveolar barrier dysfunction and overwhelming inflammation. This encompasses damage to the epithelial and endothelial layers, thickening of the interstitial matrix, edema with inactivation of pulmonary surfactant at the alveolar surface and marked inflammation mediated by infiltrating neutrophils and pro-inflammatory macrophages. For patients that survive the disease, these are the critical processes that require repair and remodeling to allow for the recovery of ARDS. As such, the current review focuses on the experimental studies that have begun to elucidate the mechanisms involved in restoring the alveolar barrier following injury.

Keywords Lung repair · Acute lung Injury · Acute respiratory distress syndrome

Overview: objective of the article

The current review focuses on lung remodeling and repair in acute lung injury (ALI) and its clinical correlate, the acute respiratory distress syndrome (ARDS). As the name implies, the damage to the lung in the setting of ARDS is rapid and includes structural damage to the alveolar endothelium, interstitium, epithelium and aqueous alveolar lining layer (hypophase and surfactant surface film). Albeit complex, the current understanding of the mechanisms leading to the damaged lung in ARDS, including downstream processes that in some cases lead to fibrosis, is substantial and has been reviewed in several excellent publications (Ware and Matthay 2000; Matthay et al. 2012; Baron and Levy 2016; Kim and Hong 2016). Less information is available about the normal mechanisms involved in repair and remodeling that occur during the recovery of ARDS, enabling the restoration of an efficient gas-exchange barrier within the lung. Nonetheless, in recent years, valuable insight has been obtained related to recovery of the epithelial layer, clearance of edema and inflammatory cells within the airspace, restoration of the interstitial matrix and repair of the endothelial layer. A review of these mechanisms will serve as the primary focus of this article.

Definition of ARDS, ALI, clinical background, causes, outcomes

ARDS was originally described in 1967 by Ashbaugh et al. (1967) in a small cohort of patients with severe hypoxemia, diffuse pulmonary infiltrates and reduced lung compliance. Since this time, the disease-specific definition has undergone several updates including the most recent in 2012, commonly referred to as the 'Berlin' definition (Ranieri et al. 2012). The current definition includes an acute onset within 1 week of a clinical insult, bilateral lung infiltrates and a reduced arterial oxygen content. The Berlin definition utilizes the oxygenation criteria with specific ventilation parameters to further classify the disease into mild (PO_2/FiO_2 between 200 and

✉ Ruud A. W. Veldhuizen
rveldhui@uwo.ca

[1] Centre for Critical Illness Research, Lawson Health Research Institute, London, ON, Canada

[2] Departments of Medicine and Physiology & Pharmacology, Western University, London, ON, Canada

300 mmHg), moderate (PO_2/FiO_2 between 100 and 200 mmHg) or severe ARDS (PO_2/FiO_2 < 100 mmHg), thereby enhancing prognostic accuracy (Ranieri et al. 2012). Of note, the term ALI, which was included in prior definitions (Bernard et al. 1994; Artigas et al. 1998), was removed in this latest definition as it was felt that this term was being utilized incorrectly to refer to a subset of patients with only mild hypoxemia, rather than as a general term to encompass all patients affected by this disease. In a broader sense, however, the term ALI remains pervasive within the literature, particularly when referring to animal models where clinical ARDS cannot be completely recapitulated.

ARDS is triggered by either direct pulmonary insults, such as gastric aspiration, smoke inhalation and pneumonia, or indirect insults, such as sepsis, pancreatitis and trauma (Ware and Matthay 2000; Matthay and Zemans 2011). However, not all individuals sustaining an initial insult will progress to meet complete diagnostic criteria for ARDS, as this threshold is highly dependent on other factors including age, premorbid alcohol consumption, or sex (Livingston et al. 1995; Johnston et al. 2003; Brown et al. 2004; Boé et al. 2009; Heffernan et al. 2011). In patients progressing to ARDS, the direct or indirect pulmonary insult leads to a series of pathological events culminating in the physiological impairment that defines the disease. Additionally, other downstream factors, such as the implementation of supportive mechanical ventilation, nutrition and fluid management, have been documented to be associated with disease progression (Santacruz et al. 2015; Bein et al. 2016; Famous et al. 2016). Mechanical ventilation in particular has been shown to significantly contribute to disease progression, especially when used with inappropriately high-tidal volumes (Brower et al. 2000; Tremblay and Slutsky 2006; Villar et al. 2011).

Despite advances in both the understanding of ARDS pathophysiology and refinements of disease definitions, effective pharmacologic interventions shown to improve patient outcomes remain lacking (Bosma et al. 2010; Matthay and Zemans 2011). Although several promising therapies have been reported in preclinical investigation or early phase clinical trials, optimal supportive care through the use of low-tidal volume ventilation strategies, or improving tolerance to ventilation strategies through pharmacologic paralysis, remain the only interventions identified to improve outcomes in larger-scale randomized clinical trials (Bosma et al. 2010; Brower et al. 2000). Overall, current data suggest that mortality among patients with ARDS remains at approximately 30 %, which is relatively unchanged over the past several years (Phua et al. 2009; Erickson et al. 2009; Villar et al. 2016).

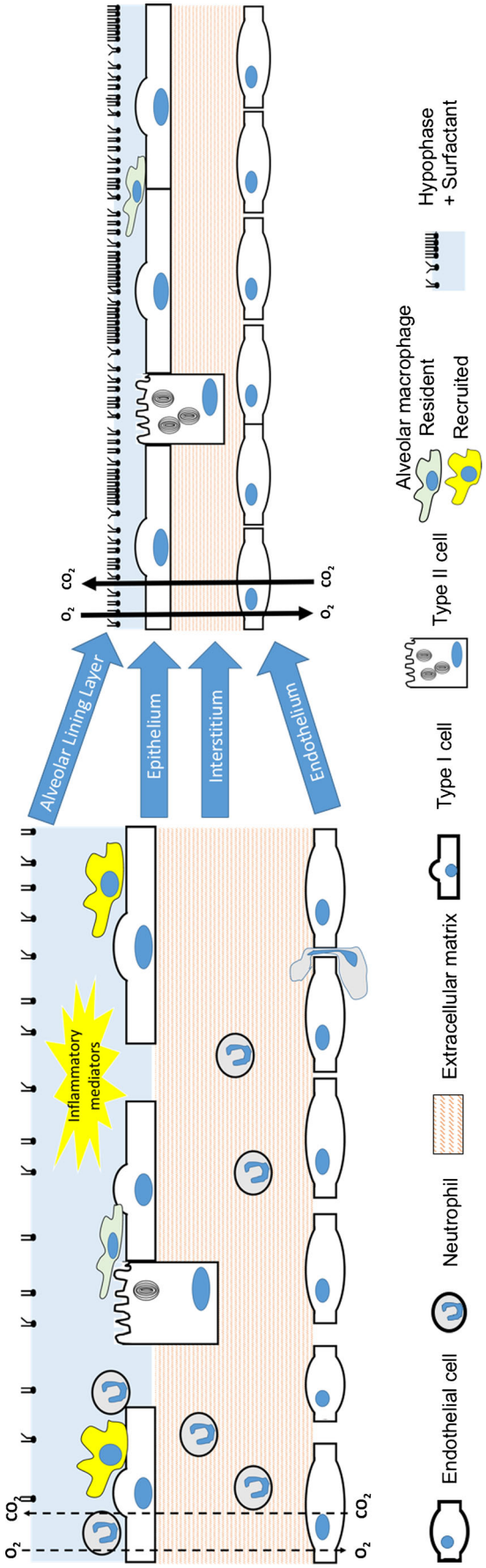
For individuals who survive to hospital discharge, long-term clinical data suggest functional impairments across a variety of neurocognitive, physical and emotional domains (Herridge 2002; Wilcox and Herridge 2011; Herridge et al. 2016; Chiumello et al. 2016). However, many of these patients may ultimately regain near normal pulmonary physiology as measured by lung function testing and chest imaging (Herridge 2002; Wilcox and Herridge 2011; Herridge et al. 2016; Chiumello et al. 2016). Implicit within this observation is the notion that individuals who survive the initial exudative phases of ARDS must be capable of initiating a resolution or remodeling process that involves an intricate and coordinated ability to reestablish an effective epithelial–endothelial barrier, while clearing residual edema fluid and residual inflammatory cells from the alveolar airspaces.

Pathophysiology of ARDS/ALI

Much of our current knowledge of ARDS pathophysiology stems from analyses of bronchoalveolar lavage (BAL) samples and post-mortem histological analysis of pulmonary tissues, as well as countless in vitro and in vivo studies (Matthay et al. 2012). As the disease involves multiple initiating insults, various susceptibility factors and potential iatrogenic factors, such as the progression of the disease through mechanical ventilation, there is no single animal model to study all pathological features of ARDS (Ranieri et al. 2012). However, to overcome the issue of wide variability among animal studies, the American Thoracic Society published recommendations of pathological and other assessments that ensure animal models accurately reflect ARDS (Matute-Bello et al. 2008, 2011). In addition to an acute onset of disease, these guidelines include physiological criteria, histological assessments, measurements of inflammation and determination of edema formation. Undeniably, these criteria provide the essence of ARDS, namely alveolar barrier dysfunction and overwhelming inflammation; these are the critical processes that require repair and remodeling to allow for the recovery of ARDS (Fig. 1) (Matthay et al. 2012). Therefore, prior to discussion of repair pathways, this section describes the primary observations made in both patients with ARDS and animal models with ALI in terms of barrier dysfunction.

Numerous clinical and experimental studies have provided insight into many of the alterations that occur in the alveolar hypophase of the lung in ARDS/ALI (Meduri et al. 1995a; Veldhuizen et al. 1995; Lee et al. 2008). Edema formation is evident in all instances of ARDS/ALI (Ware and Matthay 2000; Bhattacharya and Matthay 2013). This is determined by simple measurements of serum protein in the lavage, through dynamic measurements of leaks using a marker molecule, such as Evans blue-labeled albumin, or through measurement of the wet-to-dry ratio of the lung (Matute-Bello et al. 2011). These measurements all reflect barrier dysfunction leading to leakage of fluid and serum proteins into the alveolar space.

Analysis of BAL samples from patients with ARDS, as well as lung lavages from animal models of ALI, provide



◀ **Fig. 1** Schematic of the alveolar barrier in ARDS/ALI identifying the four distinct morphological constituents, the alveolar lining layer (including the hypophase and surfactant), epithelial layer, interstitium and endothelial cells, which require remodeling to restore the efficient gas-exchange barrier within the lung

convincing evidence of alterations in the pulmonary surfactant system (Gregory et al. 1991; Veldhuizen et al. 1995; Malloy et al. 1997; Schmidt et al. 2004). By reducing the surface tension at the alveolar surface, this endogenous lipid protein mixture is essential for maintaining normal lung compliance (Goerke 1998). In ARDS/ALI lungs, surfactant is altered, including changes in the amounts, lipid composition, protein composition and, ultimately, surface tension reducing function (Gregory et al. 1991; Veldhuizen et al. 1995; Schmidt et al. 2004). This inactivation of surfactant contributes to reduced lung compliance in ARDS, thereby directly contributing to impaired gas exchange.

Additional studies of lavage samples illustrate the other hallmark of ARDS/ALI, overwhelming inflammation (Meduri et al. 1995b; Chollet-Martin et al. 1996; Schutte et al. 1996; Nakos et al. 1998). At a cellular level, lavage samples from ARDS/ALI patients and animals demonstrate a large infiltration of neutrophils and the presence of resident and recruited macrophages, each of which may have undergone polarization to a more pro-inflammatory phenotype (Yamashita et al. 2013; Hume 2015). Associated with the cellular evidence of inflammation is a marked increase in the numerous mediators of inflammation that can be detected in the lavage sampling of the pulmonary hypophase including cytokines, chemokines, lipid mediators and a variety of other molecules (Meduri et al. 1995b; Nakos et al. 1998; de Torre et al. 2006; Lee et al. 2008; Sixt et al. 2012; Hashemian et al. 2014). Furthermore, evidence of increased oxidative stress, phospholipase and protease activity and other inflammatory pathways have been reported (Sittipunt et al. 2001; Fligiel et al. 2006; Seeds et al. 2012). These pro-inflammatory pathways, which may be initially activated as an adaptive or protective mechanism against a direct or indirect lung insult, can ultimately lead to negative consequence on the lung tissue, directly resulting in further damage of the alveolar-capillary barrier.

Histological examination of lung tissue in ARDS/ALI has demonstrated marked morphological changes of the lung associated with this disease (Ashbaugh et al. 1967; Matute-Bello et al. 2011). A hallmark feature of ARDS/ALI is a thickening of the alveolar walls and formation of hyaline membranes. These changes reflect the deposition of fibrin and other proteins, alterations to the matrix, as well as damage to endothelial and epithelial cells. In addition, the overwhelming inflammation described above is clearly evident in histological evaluation whereby abundant neutrophils can be observed (Fig. 2).

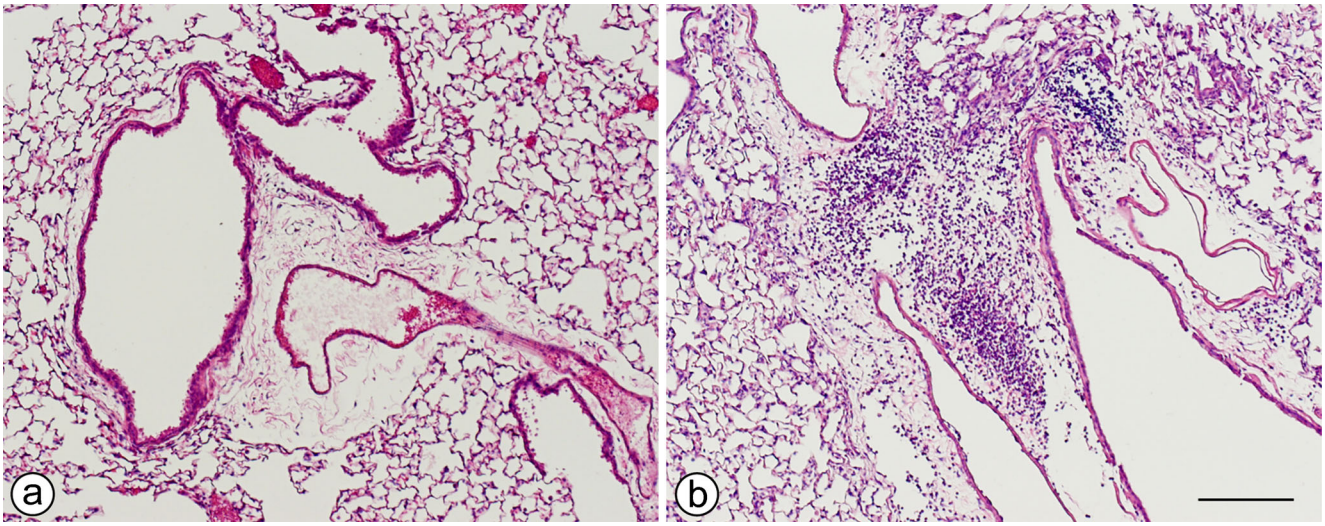


Fig. 2 Bleomycin-induced lung injury is associated with severe infiltration of leukocytes and thickening of the interstitium. Leukocyte infiltration is apparent in perivascular and interstitial spaces of the lungs of mice 3 days after intratracheal instillation of bleomycin (2.5 U/kg; **b**) vs. PBS-instilled control mice (**a**). *Scale bar* 250 μm

The microvascular barrier dysfunction associated with ARDS encompasses damage to both alveolar epithelial cells and endothelial cells. Specifically, both necrosis and apoptosis of epithelial cells during the development of ARDS has been extensively reported (Crosby et al. 2011). Elevated levels of FAS ligand (FASL) in lavage fluid from patients, combined with evidence that FAS/FASL are expressed by alveolar epithelial cells, suggests that apoptosis is at least one of the contributing factors to epithelial damage and dysfunction (Albertine et al. 2002; Lee et al. 2008). Furthermore, the presence of overwhelming inflammation affecting epithelial cells through a variety of other pathways, such as reactive oxygen species, protein and lipid mediators and protease activities, may also contribute to a loss of barrier function. Finally, the shear forces and cell stretch due to mechanical ventilation provides an additional mechanism of damage to the epithelium (Suki and Hubmayr 2014).

Similarly, pulmonary microvascular endothelial cell (PMVEC) injury, dysfunction and death are a significant component of microvascular barrier dysfunction (Groeneveld 2002). Multiple mechanisms promote PMVEC dysfunction, including activation by cytokines, mechanical interaction with activated leukocytes and exposure to harmful leukocyte-derived molecules, such as proteases and oxidants (Groeneveld 2002; Farley et al. 2008; Handa et al. 2008; Wang et al. 2012). Importantly, cell death is a critical contributor to barrier dysfunction (Gill et al. 2014, 2015). The disruption of inter-PMVEC junctions, predominantly adherens junctions comprising vascular endothelial (VE)-cadherin, is a significant component contributing to this pathology (Dejana et al. 2008; Bhattacharya and Matthay 2013). VE-cadherin is a transmembrane protein with extracellular domains that form homodimers between cells and cytoplasmic domains that link to the cytoskeleton through interaction with several partners such as p120 and β-catenin (Dejana et al. 2008; Bhattacharya and Matthay 2013). Disruption of VE-cadherin localization within adherens junctions can be due to multiple mechanisms, including degradation by metalloproteinases, physical disruption due to actin/myosin contraction leading to PMVEC retraction and potentially increased vascular endothelial growth factor (VEGF) signaling, all of which result in VE-cadherin internalization and degradation (Medford and Millar 2006; Dejana et al. 2008; Lucas et al. 2009; Chen et al. 2012; Dreymueller et al. 2012; Arpino et al. 2016).

Finally, a thickening of the alveolar wall interstitium is clearly observed histologically and is due to interstitial edema as well as to deposition of fibrin and collagen fibers, similar to wound repair in other tissues (Olczyk et al. 2014; Maquart and Monboisse 2014). The lung interstitium comprises many different cell types, including pericytes, smooth muscle cells and fibroblasts (Warburton et al. 1998). Within the interstitium is the extra cellular matrix (ECM), which includes both the basement membranes located in close proximity to the alveolar epithelium and pulmonary vasculature and the interstitial matrix (Warburton et al. 1998). The most important aspect of the interstitium within the gas-exchange unit (i.e., surrounding the alveolus) is that there is minimal interstitial matrix, with the epithelial and endothelial basement membranes fusing together (Bhattacharya and Matthay 2013). This allows for minimal distance and thereby efficient gas exchange, across the alveolar–capillary barrier (Bhattacharya and Matthay 2013). The thickening of the interstitium following lung injury caused by deposition of ECM proteins is currently the focus of intense research and the mechanisms mediating this process are the subject of ongoing debate (Rocco et al. 2001). Moreover,

there is evidence to support the involvement of multiple mechanisms. Traditionally, activation of interstitial fibroblasts to a myofibroblast phenotype, as well as epithelial-to-mesenchymal transition, have been thought to be responsible for collagen deposition following lung injury (Chapman 2011; Phan 2012). However, Hung et al. (2013) recently identified a population of pericytes responsible for collagen deposition following bleomycin-induced lung injury. Collectively, these studies demonstrate that multiple pathways are likely responsible for matrix deposition in ALI/ARDS.

Overall, ARDS is defined by histological alterations to the lung, including all components of the alveolar barrier, which lead to the dysfunction of the alveolar–capillary barrier and result in the pathophysiological impairments that define the disease (Ashbaugh et al. 1967; Ware and Matthay 2000; Ranieri et al. 2012). It should be noted that a vast number of pathological processes are involved in the generation of ARDS. Further, these processes may vary among initiating insults and also exhibit temporal variation. Description of these processes is beyond the focus of this review and readers are referred to several excellent recent review articles (Ware and Matthay 2000; Matthay et al. 2012; Baron and Levy 2016; Kim and Hong 2016).

Processes of remodeling, repair and resolution of injury

As can be deduced from the magnitude and complexity of barrier dysfunction in ARDS, remodeling and repair mechanisms to re-establish a normal alveolar surface and healthy gas exchange are equally complex and multi-factorial. This process includes the recovery of the epithelial layer, clearance of inflammatory signals and edema from the airspace, remodeling of the interstitial matrix, and repair of the endothelial layer (Fig. 1). Valuable progress has been made in all of these aspects of repair and remodeling; however, the data are limited by the experimental approaches available. To date, the data are still incomplete and too variable to create a composite picture of all of the repair processes working in conjunction to restore the normal alveolar–capillary barrier in patients who have survived the disease.

Experimental approaches

When discussing findings related to the recovery of barrier function in ARDS, it is important to understand the various experimental research approaches taken to study repair and remodeling in this disease and to realize the complexity and significant limitations associated with these approaches. As with disease development, the use of animal models can provide significant insight into cellular repair processes. However, in contrast to the development of ARDS, for which specific guidelines have been established to ensure animal models accurately reflect clinical ARDS (Matute-Bello et al. 2011), such recommendations do not currently exist for the study of repair and remodeling. In fact, the majority of experimental models used to study the exudative stages of ARDS have not been traditionally employed to study mechanisms involved in repair and remodeling. Practical factors, including the severity of the initial injury, the time frame of injury of existing ALI models and the inadequate use of prolonged mechanical ventilation strategies in laboratory animals, may represent some of the critical limitations.

The most commonly used animal model for injury/repair studies is bleomycin-induced lung injury (Kradin et al. 2004; Lawson et al. 2005). This model involves the intra-tracheal administration of bleomycin leading to marked histological changes, including significant neutrophil infiltration and inflammation 3–7 days following the insult (Fig. 2b), with subsequent development of fibrotic lesions. Interestingly, bleomycin-induced lung injury, which is one of the primary models for the study of pulmonary fibrosis, is often criticized as a model of fibrosis because mice with bleomycin-induced fibrosis resolve their fibrosis, whereas clinical pulmonary fibrosis is a progressive disease that does not resolve. Understanding the mechanisms that allow mice to recover from bleomycin-induced fibrosis may provide unique insight into the repair and remodeling mechanisms that must be initiated to allow for recovery from ARDS/ALI. Furthermore, utilizing this model in conjunction with, for example, transgenic animals or cell-based therapies, allows researchers to elucidate some of the aberrant processes that lead to fibrosis rather than repair (Madtes et al. 1999; Lawson et al. 2005; Nakagome et al. 2006; Yamashita et al. 2011). Other animal models that have been utilized to study repair generally differ from the ARDS models by inducing a less severe injury that allows for recovery. Examples of such models are the injury created by a brief period of mechanical ventilation followed by extubation (Nin et al. 2008; González-López et al. 2011) or the intratracheal or intravenous injection of lipopolysaccharide (LPS) (Yang et al. 2015; Lin et al. 2016). These types of models have the advantage of being easily titrated to a severity of injury, or, in the case of LPS, mostly provide an inflammatory injury and thereby allow for subsequent investigation into the recovery phase.

Interestingly, the one pathological feature of ARDS amendable to extensive study in vivo has been the resolution of edema (Matthay 2014). This experimental focus stems from the notion that fluid clearance after the exudative phases of ARDS reflects the cumulative effect of all repair processes. In addition, the arsenal of techniques available to study edema in ARDS is more extensive than for some other, cellular, aspects. For example, radiographic techniques, wet-to-dry lung ratios and Evans blue-labeled albumin leak readily provide simple in vivo tools to

examine edema within the injured lung, even within complex in vivo models (Matute-Bello et al. 2011).

Complementing the in vivo methods are a large number of in vitro approaches that can provide additional insight into repair processes. Both primary and transformed cell lines have been utilized to study repair mechanisms related to cell proliferation, migration and differentiation (Kheradmand et al. 1994; Geiser et al. 2001; Aman et al. 2016). In addition, co-culture systems allow investigation of either direct or indirect cell–cell interactions (Willems et al. 2013; Wang et al. 2013). Transwell cell systems that measure passage of labeled molecules across a cell layer allow the study of limiting or resolving edema formation in vitro (Wang et al. 2013; Arpino et al. 2016). These approaches can be utilized with one or multiple cell types in order to closely mimic the barrier and examine cell–cell interaction. In order to study repair mechanisms in vitro, a variety of insults can be administered ranging from the traditional wound repair scratch assay to more "ARDS-like" insults, such as exposing the primary cells to LPS, septic conditions using human plasma, or the direct administration of hydrochloric acid (Geiser et al. 2000, 2001; Wang et al. 2013; Chen et al. 2014; Arpino et al. 2016). Together, these studies have elucidated remodeling pathways and signals involved in, for example, the differentiation of a progenitor cell into a specific epithelial cell population in vitro (Gong et al. 2014; Huang et al. 2015). The obvious limitation, as with all studies of this nature, is the linkages to the in vivo situation including the 3D architectural features of the alveoli.

Recovery of the epithelial cell layer

The origin of our current understanding of the processes involved in the recovery of the epithelial cell component of the alveolar barrier stems from seminal studies by Kapanci et al. (1969) and colleagues who used a morphological approach in hyperoxia exposed monkeys to demonstrate that the alveolar type II cells were capable of proliferation and differentiation into alveolar type 1 cells. Since these studies, more evidence and more detailed insight into the progenitor role of the alveolar type II cell have been obtained.

A supportive line of evidence for the importance of type II cells in alveolar repair comes from studies utilizing type II cell transplantation (Serrano-Mollar et al. 2007; Wada et al. 2012; Guillamat-Prats et al. 2014). Two studies, using a bleomycin model of fibrosis in rats, showed improved outcomes after administration of purified alveolar type II cells. In a study by Serrano-Mollar et al. (2007), intra-tracheal instillation of freshly isolated rat type II cells 3, 7 or 15 days after bleomycin insult led to significantly reduced histological evidence of fibrosis. Utilization of male type II cells in a female model of bleomycin-induced injury allowed the authors to provide strong evidence for the engraftment of the instilled type II cells. Other studies demonstrated benefits of type II cell transplantation in an endotoxin model in piglets and in a pneumonectomy model in rats (Wada et al. 2012; Wang et al. 2016). Conversely, utilizing a transgenic mouse model with the diphtheria toxin receptor on type II alveolar epithelial cells, Sisson et al. (2010) were able to induce an injury specifically to the type II cell and demonstrated that this led to the development of pulmonary fibrosis.

While the above studies supported the role for type II cells in repair, they did not provide direct evidence for differentiation of the transplanted cells into other cell types, such as the alveolar type I cell. Evidence for this latter property of type II cells has been obtained from in vitro studies, since the differentiation of isolated type II cells into type 1 cells is observed under basic culture conditions (Shannon et al. 1992; Wang et al. 2007). In fact, in many studies focused on alveolar type II cell properties and metabolism, this transdifferentiation has actually limited the investigator's objectives. Nevertheless, this important observation of cell differentiation of type II cells in vitro has opened the door to a variety of studies examining this process in the context of remodeling/repair mechanisms (Geiser et al. 2000; Crosby et al. 2011; Xu et al. 2015). For example, Ghosh et al. (2013) used a PCR array to identify stem-cell associated genes that were altered in isolated primary rat type II cells during differentiation to type I cells; they identified IGF1, acting through upregulation of Wnt5A, as an important stimulus for differentiation. Other in vitro studies have utilized type II cell cultures and/or cell lines to establish a role of a host of mediators, including cytokines, chemokines, growth factors, metalloproteinases and lipid mediators on proliferation and differentiation (Crosby and Waters 2010). Similarly, additional studies have explored the repair role of the type II cells in in vitro scratch assays, as well as studying their interactions with other cell types such as macrophages, fibroblasts and endothelial cells (Fehrenbach 2001; Chen et al. 2014). Together, these studies provide strong evidence for the central role of the alveolar type II cell in the repair mechanisms of the lung, although the in vivo relevance of some of those observations, as well as identifying analogous findings in human cells, are eagerly awaited.

To further explore the regeneration properties of the alveolar surface, more recent studies have focused on identifying subpopulations of cells as lung progenitor cells (Fujino et al. 2011; Liu et al. 2011; Gong et al. 2014). Using lineage tracing analysis and/or various cell differentiation markers, it has been proposed that subpopulations of type II cells exist that vary in their regenerative abilities. It has also been proposed that lung-resident mesenchymal stem cells are involved in generating type II cells and are associated with alveolar repair (Hayes et al. 2015; Masterson et al. 2015). Certainly, based on many in vitro studies generating alveolar type II cells from various stem cells and experimental models of stem cell therapy, the potential of this approach has received a significant amount of recent interest (Horie et al. 2016; Cruz et al. 2016; Mei et al.

2016). However, the overall picture of the role of subpopulations of cells with regenerative properties within the lung is still somewhat blurred through the use of different markers, species and experimental models.

Endothelial remodeling

Restoration of this endothelial component of the gas-exchange barrier requires multiple steps, which include PMVEC proliferation and re-establishment of the inter-PMVEC junctions. Surprisingly, while restoration of the microvascular barrier is absolutely required for recovery from ARDS, our understanding of the mechanisms regulating this process is limited (Maniatis and Orfanos 2008; Bhattacharya and Matthay 2013). Similar to alveolar epithelial cells, proliferation of the PMVEC is required to replace the damaged and apoptotic cells (Maniatis and Orfanos 2008). The origin of these proliferating cells is the source of ongoing debate and intensive research. There is evidence that a population of resident endothelial cells (EC) within the lung, identified through a panel of markers, are capable of undergoing endothelial-to-mesenchymal transition to a highly proliferative progenitor-like cell (Suzuki et al. 2016). However, while restoration of the pulmonary microvascular barrier is dependent on proliferation of the resident EC, Mao et al. (2015) used bone marrow chimeras to generate mice expressing green fluorescent protein in bone marrow-derived endothelial progenitor cells and demonstrated that these cells are recruited to the lungs following injury. Further, these bone marrow-derived endothelial progenitor cells are also required for restoration of barrier function (Mao et al. 2015).

The mechanisms and signals involved in PMVEC proliferation and re-establishment of the inter-PMVEC junctions during repair following lung injury are currently under investigation but are less well established than in other tissues. For example, while VEGF is well known to drive EC proliferation during angiogenesis and in systemic circulation (Ribatti 2005), its role in PMVEC proliferation and restoring microvascular barrier function following lung injury is unclear (Medford and Millar 2006). VEGF is expressed by multiple cell types in the lung, including both epithelial and endothelial cells. Interestingly, there is some evidence that VEGF promotes proliferation of the alveolar epithelial cells but not the PMVEC (Papaioannou et al. 2006). In fact, it has been shown that increased VEGF expression actually promotes increased permeability across the epithelial–endothelial barrier early in the injury process, indicating not only the importance of specific signals but also the timing during the injury/recovery process (Papaioannou et al. 2006; Matthay et al. 2012). Recent studies indicate that proliferation of the resident EC may also be dependent on phosphatidylinositol-3-kinase signaling through the forkhead box M1 transcription factor, at least in an LPS-induced injury model (Zhao et al. 2006; Huang et al. 2016).

In addition to proliferation, PMVEC must also re-establish the inter-PMVEC junctions to form a leak-resistant barrier (Lucas et al. 2009; Bhattacharya and Matthay 2013). Various molecules and signaling pathways play a role in this critical process. For example, sphingosine-1-phosphate (S1P), a naturally occurring sphingolipid, is known to promote formation of adherens junctions by increasing association of VE-cadherin with α- and β-catenin (Sun et al. 2009). Specifically, S1P promotes localization of focal adhesion kinase (FAK) to the cell periphery and increased association between FAK and VE-cadherin, which suggests that the stabilization of adherens junctions and restoration of the PMVEC barrier is also dependent on increased PMVEC interaction with the ECM (Sun et al. 2009; Natarajan et al. 2013).

Metalloproteinases, including the matrix metalloproteinase (MMP) and closely related a disintegrin and metalloproteinase (ADAM) families, are known to be involved in degradation of inter-PMVEC junctions during lung injury (Alexander and Elrod 2002; Dreymueller et al. 2012). Thus, regulation of this proteolysis is likely required to allow for repair following ALI/ARDS. Recently, expression of the tissue inhibitor of metalloproteinases (TIMP) 3 by PMVEC was found to be required for establishment of PMVEC barrier function through inhibition of metalloproteinases and subsequent stabilization of inter-PMVEC cell surface VE-cadherin localization (Arpino et al. 2016). Collectively, these studies begin to provide insight into potential mechanisms regulating repair of the endothelium following ALI/ARDS; however, these few mechanisms are very likely an incomplete picture of the complex system required for endothelial repair and, as with epithelial cells, in many cases identifying analogous findings in human cells remains to be done.

Recovery of the alveolar environment

Edema

Paralleling the recovery of the epithelial and endothelial cell layer is the recovery of a normal alveolar environment, which requires clearance of alveolar edema fluid. Whereas the formation of tight barriers is essential for reducing fluid influx, active transport of fluid and ions is required to restore an air-filled airspace. Central to this process of edema clearance is the epithelial sodium channel (ENaC) and the NA/K-ATPase in both alveolar type I and II epithelial cells. The sodium transport from the alveolar space into the interstitium generated by these channels creates the osmotic pressure needed to clear water from the alveoli. The importance of these channels has been illustrated using molecular techniques, such as genetically modified mice. In mice lacking ENaC, lung fluid clearance was impaired at birth (Hummler et al. 1996).

Similarly, gene therapy using NA/K-ATPase was able to mitigate lung injury and edema formation, as assessed by protein measurements in BAL fluid and wet-to-dry ratios, in the LPS model of ALI (Lin et al. 2016). A second group of proteins that have been studied with regards to edema clearance are the aquaporins, specifically aquaporin 1 and 5, which are expressed in the alveolar epithelium (Verkman 2007). By nature of their function, these water channels were thought to assist in the clearance of edema fluid from the airspace. However, the mice genetically deficient for individual aquaporins did not support this supposition as abnormal pulmonary edema clearance was not observed following lung injury (Verkman 2007; Matthay 2014). Further studies will be required to determine the role of aquaporins in ALI/ARDS pathogenesis and repair.

Surfactant system

Considering the extensive literature available on the alterations of surfactant in ARDS (Gregory et al. 1991; Veldhuizen et al. 1995; Schmidt et al. 2004), studies characterizing the restoration of surfactant during the recovery phases of ARDS are lacking. A study by Schmidt et al. (2007), who investigated surfactant composition at several time points after diagnosis of ARDS, described improved surfactant lipid and protein composition at later (Days 7–9) as compared to earlier (Days 0–5) time-points. In addition, this study showed improved surfactant outcomes in survivors as compared to non-survivors. Beyond this study, investigations into the surfactant system in survivors of ARDS, or in animal studies during or after recovery, are limited. The assumption is that the recovery of the epithelial layer, including the surfactant producing type II cells, is necessary for the restoration of successful surfactant secretion and function.

Inflammation

Reducing a maladaptive inflammatory response associated with ARDS/ALI is not only a potential target of therapeutic strategies to reduce the propagation of ARDS but it is also important for the restorative process (Robb et al. 2016). The removal of the initiating event and/or secondary stimuli contributing to the inflammation, such as successful treatment of underlying bacterial lung infections or systemic sepsis as well as mitigation of inadvertent overstretching and collapse of the lung units due to mechanical ventilation, is an obvious essential step towards downregulating inflammation (Slutsky and Ranieri 2000; Brower et al. 2000; Santos et al. 2005). Overall, a downregulation in persistent pro-inflammatory signals, combined with the short half-life of most mediators of inflammation, allows subsequent anti-inflammatory processes to initiate repair processes.

The various alveolar macrophage populations play a central role in the resolution of ARDS and the restoration of homeostasis within the alveolar environment (Herold et al. 2011). During lung injury, two distinct populations of macrophages, resident and recruited, are present within the alveolar environment and each contributes specific roles during the resolution of lung injury (Janssen et al. 2011; Tighe et al. 2011; Johnston et al. 2012). Furthermore, these macrophages can exist in distinct polarization phenotypes: classically activated (M1) and alternatively activated (M2) macrophages (Johnston et al. 2012; Hume 2015). Whereas M1 macrophages are mostly pro-inflammatory, M2 macrophages contribute to resolution of inflammation through termination of neutrophil influx, clearance of apoptotic neutrophils and release of anti-inflammatory cytokines. Many factors can influence the balance of M1 and M2 macrophage polarization, thereby impacting repair mechanisms. As one example, it has been shown that recruited macrophages from mice lacking TIMP3 (*Timp3*$^{-/-}$ mice) are skewed towards an M1 phenotype and resistant to apoptosis, thereby leading to increased neutrophil influx following lung injury and failure to resolve inflammation (Gill et al. 2010, 2013).

In addition to the alveolar macrophages, alveolar epithelial cells play an essential role in the process of resolving inflammation. Alveolar type II cells have been termed "the defender of the alveolus" due to their broad role in maintaining a functional alveolar environment (Fehrenbach 2001). These cells can secrete inflammatory mediators, secrete surfactant, have direct cell contact with type I cells, fibroblasts, neutrophils and alveolar macrophages and interact with the ECM (Fehrenbach 2001). These properties and interactions of type II cells clearly indicate a role of this cell type in the resolution of inflammation; however, further studies are required.

Interstitium

Restoration of the alveolar wall interstitium requires a variety of processes to firstly remove residual interstitial edema and to secondarily re-establish an intact interstitial compartment through the deposition of fibrin and collagen fibers (Olczyk et al. 2014; Maquart and Monboisse 2014). Focusing on the latter, it should be noted that deposition of a provisional matrix is absolutely required for wound repair, including following lung injury. However, augmented matrix deposition or a lack of matrix remodeling can ultimately lead to pulmonary fibrosis (Gill and Parks 2008; Arpino et al. 2015). One family of potential mediators of the ECM remodeling following lung injury are the MMPs, as these proteases were initially thought to primarily degrade the ECM (Greenlee et al. 2007). However, for many of the MMPs, this may not be their main function, as many other functions have been identified for these proteases. Thus, although the MMPs more than likely play an important role in the restoration of ECM following ARDS/ALI, the specific

MMPs and/or their inhibitors, involved in restoring the interstitial matrix have not been fully established. Similarly, we have only begun to identify the mechanisms involved in the removal of proteinaceous edema fluid as well as the removal of profibrotic cells, such as the activated pericytes and myofibroblasts, from within the interstitium. Thus, in terms of regulating the processes involved in the restoration of the lung interstitium to its minimal thickness required for optimal gas exchange, much work remains to be done.

Crosstalk between repair processes

Whereas the repair of individual components of the alveolar barrier is important, the combination of all processes and the appropriate timing of repair mechanisms are required for complete restoration of lung function. As such, it is not surprising that crosstalk must therefore exist between the various repair mechanisms.

One example of crosstalk is the role of PMVEC. Although clearly important for the restoration of the microvascular barrier itself, these cells have also been found to drive recovery of other tissue compartments (Ramasamy et al. 2015). For example, VEGF stimulation of PMVECs led to increased MMP14 expression resulting in the increased release of active heparin-binding epidermal growth factor (HB-EGF)-like growth factor and subsequent activation of EGF receptor in alveolar epithelial cells (Ding et al. 2011). Ultimately, this increased EGF signaling resulted in proliferation of the alveolar epithelial cells as well as expansion of a subset of pulmonary stem cells, the bronchioalveolar stem cells (Ding et al. 2011). Furthermore, this crosstalk between pulmonary epithelium and endothelium is not unidirectional. In fact, alveolar type II epithelial cells have been found to promote PMVEC barrier function during sepsis-induced ARDS through release of a lipid mediator (Wang et al. 2013). In addition to promoting barrier function, this lipid mediator was also found to inhibit trans-PMVEC neutrophil migration, suggesting a potential role in regulating pulmonary inflammation following ARDS (Wang et al. 2013). Together, these studies highlight the importance of interaction between the different tissue compartments during the recovery from ARDS. Importantly, while we are beginning to understand the mechanisms that regulate this repair, our knowledge continues to be limited, suggesting the importance of ongoing research into these essential processes.

A more speculative form of crosstalk relates to the surfactant system. Although it is assumed surfactant recovery is related to restoration of type II cells within the alveoli, this should not imply that surfactant is an innocent bystander within the remodeling and repair paradigm. Besides the biophysical role of surfactant in reducing surface tension at the alveolar surface, which may further enhance alveolar edema resorption (Goerke 1998), individual components of surfactant, including surfactant proteins, may have a large variety of functions that could dramatically influence various repair mechanisms (Pison et al. 1994; Davies et al. 2001; Mccormack and Whitsett 2002). For example, surfactant-associated proteins A and D, SP-A and SP-D are multimeric collagen-containing C-type lectins that are components of the innate immune system (Mccormack and Whitsett 2002). Such innate properties include clearance of apoptotic cells, modulation of macrophage phenotypes, control of NETosis and regulation of pro- and anti-inflammatory signals (Ikegami et al. 1998; Palaniyar et al. 2003; Litvack et al. 2010; Phelps et al. 2011). Furthermore, when bred on specific genetic backgrounds, mice deficient in the hydrophobic surfactant protein, SP-C, have been shown to develop pulmonary fibrosis (Lawson et al. 2005; Glasser et al. 2009). It has also been reported that overexpression of TGF-β1 in mice leads to a decrease in surfactant-associated proteins that precedes formation of fibrotic tissue (Lopez-Rodriguez et al. 2016). Although these observations do not provide direct "cause and effect" relationships, they do suggest a potentially active role for surfactant in the repair mechanisms of the lung. This would also imply that impairment and compositional changes of surfactant observed in ARDS may impact the various remodeling/repair processes. Further studies to explore this possibility are required

In addition to these two examples, many other processes exist that provide signals between different compartments of the barrier, as well as appropriate signaling over the time course of the disease and its repair. For example, there is ample evidence that remodeling of the ECM by MMPs contributes to the release of various growth factors and other mediators that can impact mechanisms of repair (Parks et al. 2004; Davey et al. 2011). There is also strong evidence for crosstalk between macrophages and monocytes with epithelial cells, as well as communication between resident macrophages within different alveoli via the type I cells (Chen et al. 2014; Westphalen et al. 2014; Peteranderl et al. 2016); processes that undoubtedly impact repair functions. The injury to tissue may also directly or indirectly initiate repair mechanisms. Geiser et al. (2001) demonstrated that edema fluid from patients with ARDS had an increased epithelial wound repair activity in vitro, compared to control lavage fluid. The production of various pro-resolving mediators by, among others, epithelial cells, which directly impacts inflammatory cells, provides another mechanism of crosstalk and the initiation of the repair processes (Xie et al. 2013; Basil and Levy 2016). Together, these studies illustrate the intricacy of the repair processes and the obvious need for further studies in various animal models reflecting ARDS as well as in clinical samples.

General perspective and implications for clinical management

From a clinical perspective, ARDS remains a challenging enigma from which neither experimental findings nor clinical trials have yielded significant strides in terms of therapeutic

advances (Bosma et al. 2010). The inception of the NHLBI-sponsored ARDS Network (ARDSnet) in the 1990s attempted to translate a wealth of molecular and basic science knowledge into reduced ARDS-associated morbidity and mortality by conducting several multi-center randomized clinical trials (Brower et al. 2000; Dinglas et al. 2015; Lammi et al. 2015; Semler et al. 2016). Although these trials and studies yielded important information on methods by which supportive care for these patients should be delivered (including lower-tidal volume mechanical ventilation or medical paralysis), no studies, including other non-ARDSNet clinical trials, have demonstrated a benefit from any pharmacologic intervention (Brower et al. 2001; Bosma and Lewis 2007; Bosma et al. 2010; Baron and Levy 2016). Over the past number of years, and following the termination of the ARDS Network, a newer NHLBI-sponsored initiative has sought to identify and potentially prevent the development of ARDS in high-risk patients based on the postulation that therapies targeting mid- to late stages of the disease process may be administered at a refractory stage of the disease. This clinical network for the Prevention and Early Treatment of Acute Lung Injury (PETAL) will focus on early intervention as a means of delivering targeted therapies to high-risk individuals (www.http://petalnet.org/). To date, results stemming from PETAL-sponsored studies have not been reported.

In contrast to those mechanisms that govern proximal events related to ARDS susceptibility, other lines of investigation, such as those identified in the current review, seek to identify more distal processes within the ARDS time-course that may be of equal importance in terms of therapeutic development. At this stage, the translation of this body of knowledge into improving clinical outcomes remains a fundamental challenge. A major factor complicating this approach is the inherent limitation of the available in vitro or in vivo experimental systems not accurately reflecting a widely heterogeneous and dynamic disease process. The ability to either hasten or promote homeostatic repair/remodeling in a diseased lung after the onset of ARDS may be further contingent upon clinical factors and/or in vivo biomarkers that allow for the identification of specific patient populations combined with optimal timing and delivery of therapy. Despite these hurdles, considerable progress has been made in understanding the highly coordinated complex series of events by which lung remodeling or repair processes may ensue. Therapies aimed at enhancing these endogenous mechanisms to direct the lung toward recovery may well provide a novel approach to therapy for this complex disease. Coordinated and continued efforts between basic and clinical researchers will be required to translate this approach into a clinical reality.

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