Therapeutic targeting of acute lung injury and acute respiratory distress syndrome

THEODORE J. STANDIFORD, and PETER A. WARD

ANN ARBOR, MICH

There is no Food and Drug Administration-approved treatment for acute respiratory distress syndrome (ARDS), in spite of the relatively large number of patients with the diagnosis. In this report, we provide an overview of preclinical studies and a description of completed and future clinical trials in humans with ARDS. Preclinical studies dealing with acute lung injury have suggested roles for complement and complement receptors, as well as the evolving role of histones, but details of these pathways are inadequately understood. Anti-inflammatory interventions have not been convincingly effective. Various cell growth factors are being considered for clinical study. Interventions to block complement activation or its products are under consideration. Stem cell therapies have shown efficacy in preclinical studies, which have motivated phase I/II trials in humans with ARDS. (Translational Research 2016;167:183–191)

Abbreviations: AEC = alveolar epithelial cell; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; BALF = bronchoalveolar lavage fluid; DAMPs = danger-associated molecular patterns; GM-CSF = granulocyte-macrophage colony-stimulating factor; IR = ischemia-reperfusion; LPS = lipopolysaccharide; NETs = neutrophil extracellular traps; PAMPs = pathogen-associated molecular patterns; PMNs = polymorphonuclear leukocytes (neutrophils); TLRs = toll-like receptors

EPIDEMIOLOGY OF THE ACUTE RESPIRATORY DISTRESS SYNDROME

The acute respiratory distress syndrome (ARDS) is characterized by a severe, acute inflammatory responses within the lung, resulting in diffuse damage to the alveolar-capillary barrier, flooding the airspaces with protein-rich edema fluid, with resulting severe gas-exchange abnormalities.[1,2] This is a common syndrome, with an annual US incidence of greater than 80 per 100,000 population, and especially common in the elderly.[3] ARDS can be precipitated by either direct or indirect insult to the lung. Direct insults include pneumonia, aspiration of gastric contents, pulmonary contusion, or inhalation of injurious gases. Indirect injury can occur as a result of systemic processes such as sepsis, pancreatitis, multiple trauma, or massive transfusion of blood products. Sepsis is the most common cause of ARDS in humans. Sepsis because of a pulmonary cause carries with it the highest mortality compared with other etiologies of ARDS.[3] Early deaths in ARDS are because of hypoxic respiratory failure and development of multiple organ failure, whereas deaths after 2 weeks are usually attributable to progressive pulmonary dysfunction as a result of exuberant fibroproliferation and the development of nosocomial infection, most notably pneumonia.[4,5]

From the Department of Internal Medicine, Pulmonary and Critical Care, University of Michigan Medical School, Ann Arbor, Mich; Department of Pathology, University of Michigan Medical School, Ann Arbor, Mich.

Submitted for publication March 18, 2015; revision submitted April 27, 2015; accepted for publication April 29, 2015.

Reprint requests: Peter A. Ward, Department of Pathology, University of Michigan Medical School, 1301 Catherine Road, Ann Arbor, MI 48109-5602; e-mail: pward@umich.edu.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2015.04.015

PATHOGENESIS OF ARDS

In the initial phase of ARDS (referred to as the exudative phase), direct or indirect insults generally result in

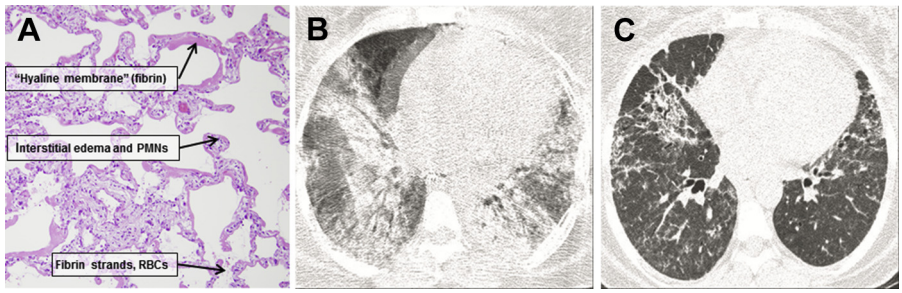

Fig 1. Histologic and radiographic features of ARDS. (**A**) Lung from a patient with ARDS, stained with hematoxylin and eosin. There are prominent "hyaline membranes" consisting of fibrin deposits along alveolar walls, widespread interstitial edema accompanied by neutrophils. Alveolar spaces also contain RBCs and fibrin strands. Panels (**B**) and (**C**) are radiographic appearances of exudative and fibroproliferative phases of ARDS. The exudative phase is characterized by diffuse ground glass and alveolar opacities, whereas the fibroproliferative phase is characterized by residual linear opacities, traction bronchiectasis, and honeycombing. ARDS, acute respiratory distress syndrome; PMN, polymorphonuclear leukocytes (neutrophils); RBC, red blood cells.

injury to both the capillary endothelium and the alveolar epithelium.[6,7] Type I alveolar epithelial cells (AECs) comprise >95% of the alveolar surface, and are particularly susceptible to injury. As a consequence of capillary endothelial and AEC injury, there is loss of alveolar-capillary barrier function and accumulation of protein-rich edema fluid within the pulmonary interstitium and alveolus.[1] Denuded epithelium is replaced by the formation of proteinaceous hyaline membranes (Fig 1, *A*). The exudative phase of ARDS is temporally associated with influx of neutrophils within pulmonary capillaries, margination and adherence to the activated endothelium, followed by exuberant accumulation of polymorphonuclear leukocytes (neutrophils) (PMNs) in both interstitial and alveolar spaces.[8] Activated PMNs contribute to lung injury by releasing a variety of injurious molecules, including neutrophil elastase, metalloproteases, and other proteolytic enzymes, oxidants, and reactive nitrogen species.[9,10] In addition to PMNs, there is chemokine-dependent emigration of macrophages, which can amplify pulmonary injury by releasing inflammatory cytokines and apoptosis-inducing molecules.[11]

The fibroproliferative phase of ARDS occurs early after injury (within initial 3 days) and temporally overlaps with inflammatory events that characterize the exudative phase. The alveolar space becomes engorged with proliferating mesenchymal cells, including fibroblasts, myofibroblasts, and locally generated pluripotent mesenchymal progenitor cells.[12,13] Type II AECs proliferate to replace necrotic and apoptotic type I cells, and new blood vessels form within the provisional matrix. There is also evidence of thrombogenesis and impaired fibrinolytic activity, as indicated by the accumulation of fibrin in the distal airspaces, together with microthrombi in small pulmonary vessels.[14-16] In some patients, there is pronounced deposition of matrix components, including fibronectin and replacement of type III collagen by type 1 collagen.[12] An exuberant fibroproliferative response in patients with ARDS is associated with a requirement for prolonged mechanical ventilation and increased mortality.[5,17] The computed tomography appearance of the exudative and fibroproliferative phases of ARDS is shown in Fig 1, *B* and *C*, respectively.

ANIMAL MODELS OF ACUTE LUNG INJURY

No animal model recapitulates all the key histopathologic features of human ARDS. However, a number of models of acute lung injury (ALI), mostly in rodents, have been described and are outlined in Table I, along with the routes by which the various ALI-inducing agents are given. It has been suggested that agents in items 1a–d tend to be associated, at least early on, with damage of capillary endothelial cells in lungs.[18-20] These agents include oleic acid, which is known to be toxic to vascular endothelial cells.[21] Lipopolysaccharide (LPS), which is not directly toxic to cells, produces a sequence of events that can lead to both endothelial cell and alveolar epithelial damage. Live *Escherichia coli* given via the airways produces a series of events in lung similar to the effects of LPS. Bleomycin causes injury to endothelial cells, usually with resultant fibrosis through a series of signaling pathways involving transforming growth factor beta and other signaling molecules. Agents cited in 2e–k (Table I) are thought to chiefly target AECs, at least in the early phases of lung injury. HCl given i.t. will cause reversible damage to the alveolar epithelium, although in the case of aspiration pneumonia in humans, there is an abundance of particulates (from ingested food) that produce a much more pleomorphic and intense inflammatory response than that caused by HCl alone. A more recently