Failure of Lung Repair Following Acute Lung Injury*
Regulation of the Fibroproliferative Response (Part 1)

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ACUTE LUNG INJURY (ALI) can be defined as a rapid alteration of the alveolar wall leading to impairment of the gas exchange apparatus following exposure to noxious environmental or endogenous agents. Clinicians from nearly all disciplines regularly confront this problem. Acute lung injury can range in severity from the modest and reversible biochemical and functional impairment observed following exposure to 100 percent oxygen for relatively brief periods1 to the devastating respiratory failure of the adult respiratory distress syndrome (ARDS), the most severe form of acute lung injury, with its attendant mortality of up to 70 percent.2 Nationwide, approximately 100,000 patients die each year with this syndrome.

Despite apparent similarities in the severity of the initial injury and aggressive, sophisticated supportive modalities, patient outcomes vary from rapid death due to respiratory insufficiency to complete recovery. Although this spectrum of outcomes can be discerned in retrospect, the ability to predict the course and prognosis in an individual patient has been elusive. The excellent epidemiologic investigations that have attempted to predict outcome have focused primarily on clinical and laboratory parameters measured at or near the onset of lung injury as predictors of survival or death. For example, age and specific risk factors for ALI (eg, sepsis and trauma) are clinical determinants of survival following ALI.3 However, events occurring after the onset of lung injury may be equally important in determining patient outcome. For example, the early onset of the “multiple organ failure syndrome” (MOFS) after ALI adversely affects prognosis.4 In addition, prompt control of the inciting event leading to lung injury, referred to as “source control” (eg, elimination of a septic focus), is a prerequisite for eventual recovery. Even when source control can be accomplished, however, patient outcomes vary from complete recovery to death. This variability derives in large part from the effectiveness of lung repair, which ranges from complete restoration of the gas exchange apparatus to an acute fibroproliferative response in the air spaces and vessel walls. This fibroproliferative response results in profound and progressive hypoxemia and severe pulmonary hypertension necessitating prolonged mechanical ventilatory support.

Current concepts of the sequelae of lung injury and the events leading to acute alveolar and microvascular fibrosis are derived from detailed morphologic examination of the lungs from patients dying after ALI. In these studies, a common anatomic theme emerges: there is a striking accumulation of mesenchymal cells and their connective tissue products in the alveolar airspace and in the walls of intra-acinar microvessels,5,6 ie, an acute fibroproliferative response.

In an effort to unravel the complex cellular and molecular events determining whether repair or fibrosis occurs, our discussion by necessity begins with a clinical classification of ALI. The classification reflects differences between patients in terms of source control and the distinct hospital courses that clinicians observe. These clinical events will be correlated with the anatomic changes characterizing effect repair as well as acute fibrosis. In the second part of the review we will examine the current state of knowledge regarding the molecular signals that direct the fibroproliferative response. While conceptually of equal importance to a thorough understanding of patient...
outcome, a detailed consideration of the molecular signals involved in reepithelialization of the air-lung interface and reendothelialization of the blood-lung interface are beyond the scope of this review. A more precise understanding of the fibroproliferative process following ALI will hopefully form the foundation for devising effective therapeutic interventions designed to enhance lung repair.

Clinical Classification of Acute Lung Injury

Acute lung injury causes rapid structural alterations in the gas exchange apparatus. These changes become manifest in the patient as the constellation of clinical and physiologic aberrations comprising acute respiratory insufficiency. These aberrations are best described in patients with ARDS. However, it is likely that similar physiologic changes occur to a lesser extent in individuals with milder forms of ALI. Clinically, the earliest sign of lung injury is tachypnea, which may precede the onset of dyspnea by hours or even days. At this stage the patient has an increased alveolar-arterial O₂ difference (P[A-a]O₂) and the chest roentgenogram usually shows increased interstitial markings, reflecting interstitial pulmonary edema. As the injury progresses, alveolar flooding leads to frank hypoxemia and diffuse alveolar opacities on the chest roentgenogram. The hypoxia in these patients is difficult to overcome with increased inspired oxygen tensions due to the microanatomic shunting of blood resulting from a combination of alveolar flooding and collapse. In addition to the shunting of blood, gas exchange is also adversely affected by the increased dead space ventilation resulting from microvascular injury leading to thrombosis. Within a few hours of the onset of ALI, pulmonary vascular resistance begins to rise. Mild pulmonary hypertension is uniformly present in ARDS as a result of this elevated pulmonary vascular resistance. In more severe forms of ALI, patients develop moderate to severe pulmonary hypertension as the pulmonary vascular resistance reaches approximately two to three times the normal value. Thus, patients with ALI demonstrate varying degrees of shunt physiology, dead space ventilation, and pulmonary hypertension.

In addition to the pulmonary abnormalities, signs of systemic illness may be present, including fever, decreased systemic vascular resistance, increased cardiac output, and hypermetabolism. This constellation of findings, referred to as the “sepsis syndrome,” may or may not be associated with an identified source of infection. When a source of infection can be identified early in the course of ARDS, this source is frequently intra-abdominal. The source of sepsis syndrome occurring late in the clinical course of lung injury remains unclear in many cases. Although bacterial pneumonia accounts for some of these cases, the inability to clearly diagnose a lung infection in these patients is common. The hypothesis that noninfectious mediators of sepsis syndrome and multiple organ failure such as interleukin 1 and tumor necrosis factor (TNF) are being produced and released into the circulation by the injured lungs is an active area of investigation. For example, TNF concentrations are elevated in the plasma of patients with sepsis and high concentrations of TNF have been detected in the lower respiratory tract of patients with ALI. These observations suggest a possible pathogenic role for local pulmonary TNF production in the sepsis syndrome characteristic of ALI.

After a catastrophic clinical event, ALI may occur as an isolated organ failure or as a component of MOFS, a systemic disorder characterized by concurrent or sequential failure of the coagulation system, liver, kidneys, and brain. When MOFS is present at the onset of ALI, the prognosis appears to be considerably worse than in patients with ALI alone. When ALI occurs as an isolated organ failure, patients can be classified into one of five general groups based on their clinical course (Fig 1).

In group 1 patients, the source leading to ALI (eg, a septic focus) is not controlled. Control of the source of the injury appears to be of critical importance in determining the outcome of ARDS. The term “source control” may take on various meanings depending on the clinical context. For example, after multiple systems trauma, source control might include fluid and blood resuscitation and stabilization of skeletal injuries; while in the setting of postoperative gram-

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**Figure 1.** When acute lung injury (ALI) occurs as an isolated organ failure, patients follow one of several distinct clinical courses. When the source of the injury is not controlled, multiple organ failure syndrome (MOFS) ensues, leading to death. Even when the source is controlled, however, the clinical courses and outcomes span a wide spectrum. This diversity reflects differences in the alveolar repair process occurring after ALI. ARDS = adult respiratory distress syndrome.
negative sepsis, appropriate source control would include abscess drainage and systemic antibiotics. Patients in whom source control is not accomplished in the first few days after onset follow a progressively deteriorating course characterized by advancing respiratory insufficiency and uncontrolled sepsis syndrome, leading invariably to MOFS and death.

Those patients in whom the initial source leading to ALI is controlled follow one of four clinical courses. Group 2 patients develop all the classic physiologic hallmarks of ALI and may even develop sepsis syndrome. However, these patients rapidly recover, usually within seven to ten days, apparently without permanent lung dysfunction. The common feature in this group of patients is that source control is accomplished early after the onset of injury, and recurrent events predisposing to further lung injury do not occur. Although direct anatomic evidence is lacking, the rapid recovery of lung function is these patients suggests that extensive fibroproliferative changes have not supervened during the first few days following lung injury.

Group 3 patients are those who suffer a more prolonged period of respiratory insufficiency than those in Group 2, but who ultimately recover from the ALI. Although these patients may require a prolonged period of ventilatory support, sometime within the first few weeks after the onset of lung injury, a slow improvement in gas exchange is seen. If sepsis syndrome is present, its resolution is marked by disappearance of fever, lessened hypermetabolism, a decrease in the cardiac index, and normalization of the systemic vascular resistance. The minute ventilation requirement for CO$_2$ elimination is decreased, due both to decreased dead space ($V_{d}/VT$) and to decreased CO$_2$ production. At the time of extubation, these patients continue to have decreased lung compliance and an increased P(A-a)O$_2$. Over the ensuing months, a progressive improvement in pulmonary mechanics occurs; by one-year postextubation, many patients will have a normal or near-normal total lung capacity, vital capacity, and forced expiratory volume in 1 s (FEV$_1$). Others have persistent mild restrictive ventilatory defects. By that time, most patients have near-normal chest roentgenograms, although mild symptoms of cough, dyspnea, or wheezing may persist. Despite the restitution of normal lung mechanics, evidence of abnormal gas exchange persists. Survivors have reduced pulmonary diffusing capacity, which may continue to improve slowly with time. Whether ongoing sepsis syndrome is caused by the injured lungs that are incapable of effective repair or creates a milieu in the alveolar microenvironment conducive to a progressive fibroproliferative response is currently unknown. In either case, it is clear that in this group of patients, effective lung repair does not occur. Improving the outcome of this group of patients will require a better understanding of the cause and nature of the sepsis syndrome, as well as the development of interventions that promote effective lung repair.

Group 5 patients, a relatively small group, have a rapidly progressive downhill course marked by decreasing lung compliance and worsening hypoxemia resulting in death from respiratory failure, usually in less than one week. Even when gas exchange is accomplished late in the course of the illness by using extracorporeal membrane oxygenation, lung repair does not occur. The possibility that permanent derangements of lung function may be ameliorated by
the early institution of nonventilatory gas exchange is being explored. Autopsies on this group of patients have shown a striking degree of intra-alveolar fibrosis occurring within a week of the onset of illness. Devising therapeutic strategies for this group will depend on a better understanding of the factors regulating the rapid development of alveolar fibrosis.

Thus, following ARDS, the most severe form of ALI, an initial severe impairment of lung mechanics and gas exchange occurs. This may occur in isolation or as part of the MOFS. Control of the source of injury is a key factor in influencing outcome in patients with ALI. However, even after source control is achieved, a fibroproliferative process characterized by intra-alveolar and microvascular fibrosis may supervene. In some patients, this fibroproliferative process appears to be at least partially reversible and does not preclude effective repair of the alveolus. In others, it is progressive and fails to abate. Significantly, our current supportive therapies for ALI do not specifically target this fibroproliferative process. In addition, based on inferences from studies of bone and wound healing, the high pressure and high stretch ventilatory strategies commonly used to support these patients may actually promote fibroproliferative change by interrupting reepithelialization of the air-lung interface. An improved understanding of the cellular and molecular events determining whether repair or fibrosis will occur is critical for clinicians to devise strategies to improve the outcome of patients following ALI.

To understand whether effective repair of the gas exchange apparatus will occur or whether lung repair will be subverted by an acute fibroproliferative response, it is necessary to review key aspects of normal and pathologic alveolar and microvascular anatomy. This will serve as the starting point for consideration of how mesenchymal cell growth factors and chemotacticants might play a role in the pathogenesis of the fibroproliferative process following ALI.

NORMAL ALVEOLAR ANATOMY

Air-Lung Interface

The alveolar epithelium is comprised almost exclusively of type I and type II cells. Type I epithelial cells are flat with attenuated cytoplasm and few subcellular organelles. Type II epithelial cells are cuboidal and possess microvilli on their apical surface. Although type II cells outnumber type I cells by a ratio of 2:1, type I cells cover 95 percent of the air-lung interface. Type II cells contain cytoplasmic lamellar bodies and are responsible for the production of pulmonary surfactant. In addition, type II cells are the progenitor cells of the alveolar epithelium, capable of replicating to replace cells that are lost following injury. The interstitium is that region of the alveolar wall bounded by and including the epithelial and endothelial base-

ment membranes. It consists of cells and stroma as well as the two basement membranes. The predominant cellular constituents of the interstitium are mesenchymal cells. Also present within the interstitium are immune and inflammatory cells, including macrophages with a few lymphocytes. Neutrophils are rarely found in the normal lung. The stroma is comprised of several classes of connective tissue macromolecules, including collagens type I and III, elastin, fibronectin, and proteoglycans. The connective tissue elements of the basement membranes include type IV collagen, laminin, and fibronectin. Over a large portion of the gas exchange surface, the endothelial and epithelial basement membranes are a single fused structure virtually excluding additional elements of the interstitial space from this portion of the alveolar wall. The interstitium serves as a scaffolding for the remaining parenchymal elements defining the general outline of the alveolar structures.

Blood-Lung Interface

The pulmonary microvessels enter the acinus as muscularized arterioles (external diameter, approximately 150 \(\mu m\)) and gradually arborizing until they appear as typical capillaries (external diameter, approximately 15 \(\mu m\)) within the alveolar wall. Smooth muscle cells and pericytes are the primary mesenchymal cell constituents of the vascular wall. The alveolar capillaries are typical microvascular structures with a single nonfenestrated endothelial cell layer connected by tight junctions resting on a basement membrane.

ANATOMY AND PATHOGENESIS OF THE FIBROPROLIFERATIVE PROCESS FOLLOWING ACUTE LUNG INJURY

There are two principal structural changes that characterize the fibroproliferative process following ALI: (1) a striking accumulation of mesenchymal cells within the alveolar airspace and (2) a markedly expanded media and intima of precapillary microvessels resulting in a decreased luminal diameter of vessels (Fig 2). Our current understanding of the sequelae of lung injury and the events leading to acute lung fibrosis are derived from detailed morphologic studies in animal models and of patients in whom biopsy material was available. The following discussion will examine the morphologic features and pathogenesis of the fibroproliferative response following ACI at the air-lung interface and the blood-lung interface.

Air-Lung Interface

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patients. Within hours of the onset of lung injury, the air-lung interface is denuded as type 1 epithelial cells die. Within a few days after this epithelial injury, there are intra-alveolar accumulations of mesenchymal cells, macrophages, and inflammatory cells. The interstitium is expanded with increased numbers of mesenchymal cells and numerous collagen fibrils and elastic fibers. The epithelial basement membrane develops gaps, leaving the disrupted interstitium in direct communication with the alveolar airspace. When effective repair ensues, there is timely migration and replication of type 2 epithelial cells repopulating the denuded air-lung interface. In striking contrast, when acute fibrosis supervenes, activated myofibroblasts from the interstitium migrate into the alveolar airspace through these gaps in the basement membrane and attach to the luminal surface of the damaged basement membrane. Myofibroblast replication at the air-lung interface eventually obliterates the gas exchange unit. Immunohistochemical studies reveal increased amounts of fibronectin in the airspace, predominantly in areas of intra-alveolar fibrosis and on the surface of hyaline membranes.

Biochemical analysis indicates there is also an accumulation of collagens type I and III in the expanded interstitium. Type III collagen predominales in the alveolar septae and interstitium early following lung injury, whereas type I collagen is the major collagen present in the later stages. In addition, there is filling of the alveolar airspace by collagens similar to those present in the adjacent interstitium.

Blood-Lung Interface

At the blood-lung interface, there are dramatic alterations in the normally nonthrombogenic pulmonary endothelium so that intravascular coagulation ensues. The resultant platelet and leukocyte aggregation, in conjunction with molecules that mediate inflammation and cellular injury, lead to endothelial cell dysfunction and death. This interrupts circulation to the gas exchange unit, resulting in the markedly increased dead space and minute ventilatory requirements characteristic of these patients. Morphologically, endothelial cells become separated from their basement membrane and the number of patent capillaries decreases. When an effective pulmonary circulation is to be reestablished, endothelial cell replication along the structural framework provided by the denuded basement membranes apparently ensues. Although the exact microanatomy in the reconstituted lung of patients surviving ACI remains to be detailed and direct hemodynamic measurements are lacking, the recovery of nearly normal lung function in some of these patients suggests that effective reconstitution of the blood-lung interface has occurred. In marked contrast, in many patients failure of effective vascular repair occurs, leading to progressive pulmonary hypertension. This is in marked contrast, in many patients failure of effective vascular repair occurs, leading to progressive pulmonary hypertension. In this circumstance, there are dramatic alterations in vascular mesenchymal cell number and distribution. Light microscopic studies of lung tissue from patients dying of ARDS reveal focal microvascular obstruction caused by excess numbers of mesenchymal cells in the intima of the arterial wall. In addition, the media is widened by increased numbers of smooth cells, collagen, and mononuclear cells. Thus, the fibroproliferative process following ALI features mesenchymal cell migration, replication, and the accumulation of connective tissue products in the alveolar airspace and vascular wall, leading to ablation of the gas exchange apparatus. This results in a fibrotic, noncompliant lung that is incapable of efficient gas exchange. In the second part of this review, we will discuss the current state of knowledge regarding the mesenchymal cell response and the molecular signals that direct the fibroproliferative response.
ACKNOWLEDGMENTS: We would like to thank Sylvia Danielson for her excellent assistance in the preparation of this manuscript.

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