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Understanding ARDS-associated fibroproliferation

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Understanding ARDS-associated lung fibroproliferation requires viewing (1) ARDS as a disease of multifactorial etiology and not as a syndrome and (2) fibroproliferation as an integral part of the disease process and not as a separate temporal component. Although the term "syndrome" (aggregate of symptoms and signs) was applied in its original description [1], ARDS meets all the constitutive elements of a disease process [2]. Translational clinical research has constructed—through a "holistic" level of inquiry—a pathophysiological model of ARDS that fits the pathogenesis (biology—core stratum) with morphological (histology—intermediate stratum) and clinical (physiology—outer stratum) findings observed during the course of the disease [3].

Fibroproliferation is an integral component of the tissue defense response (TDR), a stereotypical host reaction to contain—at the tissue level—insults and repair any resultant injury. The TDR (constituent of innate immunity) consists of a highly organized and integrated network of three simultaneously activated pathways [3]—tissue inflammation (permeability of the microvasculature with exudative edema, increased expression of adhesion molecules and leukocyte extravasation, and release of leukocyte products causing tissue damage), hemostasis (intravascular clotting and extravascular fibrin deposition; inhibition of fibrinolysis), and tissue repair (regenerating native parenchymal cells, fibroproliferation and deposition of the extracellular matrix) [3]. In ARDS and multiple organ dysfunction, the effects of systemic inflammation on circulating and tissue cells drive the tissue defense response in the lungs and vital organs. Systemic inflammation is activated by the master regulator of the innate immunity, the ancient nuclear factor-κB (NF-κB) signaling system [4], and downregulated by the end product of the (systemic inflammation-activated) HPA axis, the activated glucocorticoid receptor α (GRα) [5].

The distinct anatomical unit of the lung involved in ARDS is the pulmonary lobule, the smallest discrete visible portion of the lung (~2 cm), surrounded by connective tissue septa. Within each lobule there are 3–5 terminal bronchioles leading to the acinus (respiratory bronchioles, alveolar ducts, alveolar sacs). In ARDS, every anatomical component—epithelium, endothelium, and interstitium—of the entire pulmonary lobule is involved, including the respiratory bronchioles, alveolar ducts, and intraacinar arteries and veins [6]. In the lung, efficient gas exchange requires a minimal diffusion distance between the alveolar air and blood and a large surface area (70–100 m^2) [6]. For this physiological purpose, endothelial cells and type I pneumocytes have an attenuated cytoplasm, making them particularly susceptible to injury [6].

The histological hallmark of ARDS, "diffuse alveolar damage" (DAD) [7], is classically differentiated in two major temporal phases: exudative (early) followed by fibroproliferative (late), with the latter potentially evolving into fibrosis. The exudative phase is characterized by "diffuse" injury across the alveolar-capillary membrane (ACM) resulting in (1) edema of the air spaces and

interstitium with an inflammatory (protein- and neutrophil-rich) exudate, (2) hyaline membrane formation (extravascular fibrin deposition) over denuded type I alveolar epithelial cells, and (3) clotting within intraacinar injured microvessels (decreased capillary density). The proliferative phase of DAD is characterized by the partial replacement of damaged epithelial and endothelial cells and the striking accumulation of mesenchymal cells and their connective tissue products in the interstitium, air spaces (through epithelial gaps), and walls of the intraacinar microvessels (through endothelial gaps) [6].

A series of studies involving lung tissue (biopsy and autopsy), high-resolution CT (HRCT) scan images, and laboratory measurements (blood and bronchoalveolar lavage) of markers of inflammation and fibroproliferation have shown that both exudation and fibroproliferation coexist in different proportions throughout the disease process. Histologically, these two processes can be seen adjacent to each other and have been described in detail [6]. While fibroproliferation—based on histological findings (fibroblast migration, proliferation, and deposition of collagen)—was initially recognized as a late event, it is now well proven that fibroproliferation and collagen deposition are in full motion at ARDS onset. This is supported by multiple clinical studies including a landmark large autopsy series [8], HRCT findings at ARDS onset [9], and serial measurements of plasma and bronchoalveolar (BAL) procollagen [10]. Similarly, exudative changes are not exclusive to early ARDS [6], but are found throughout the course of the disease [8, 11].

The onset of ARDS is preceded (24–72 h before) by the release into the systemic circulation of the proximal mediators of inflammation from a pulmonary (direct) or extrapulmonary (indirect) source. The lung—the organ with the largest vascular surface—becomes affected; the involvement is diffuse but spatially inhomogeneous. Thousands of lobules are initially involved while thousands are spared, with a higher degree of systemic inflammation leading to more widespread and severe involvement. When we view a single affected lobule, the progression by day 7 is from exudation to fibroproliferation. However, when we view a whole lung at day 7, we observe lobules that are at different evolutionary stages (Fig. 1) based on the time of initial involvement. Since exudation and fibroproliferation coexist during the disease, a more precise and clinically relevant way to describe the histological and clinical (parentheses) progression of ARDS is adaptive (resolving) vs. maladaptive (unresolving). The intracellular relationship (nuclear binding) between NF-κB and GRα in lung tissue and circulating cells is the central driving factor in the adaptive vs. maladaptive evolution of ARDS [5]. In lung biopsies, histological sections with severe vs. mild fibroproliferation had higher nuclear uptake of NF-κB than GRα [5].

An NF-κB-driven response (Table 1) [5]—with continued release of inflammatory mediators (dysregulated

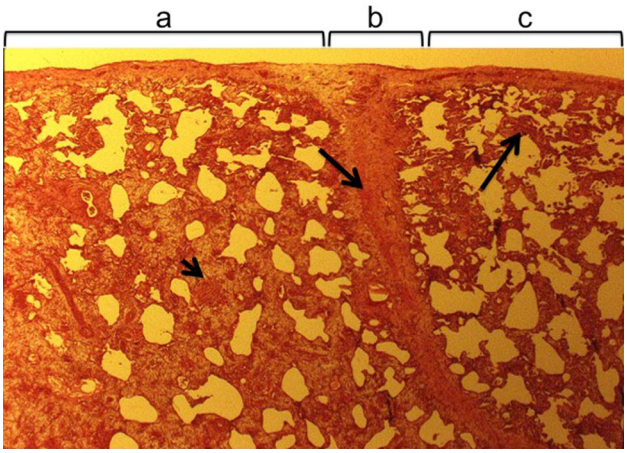

Fig. 1 Photomicrograph of lung tissue obtained after 7 days of mechanical ventilation in a patient with unresolving ARDS (maladaptive response). The interlobular septa (**b**) divide two lobules at different evolutionary stages based on the time of initial involvement. Section (**a**) shows extensive interstitial, inter- and intraalveolar, fibroblastic and myofibroblastic proliferation and mononuclear inflammatory cells resulting in marked widening of interalveolar and interlobular septae and subpleural tissue widening. In addition, there is evidence of intravascular thrombosis of some of pulmonary arterioles (*arrow*) and occlusion of the pulmonary venules and lymphatics in the widened interlobular septa (*arrow*) and subpleural tissue. The arrow in section (**c**) points to the fibrinous exudate along the alveolar wall

systemic inflammation) over time—sustains neutrophil activation with recurrent tissue injury, intra- and extravascular coagulation (exudation) in previously spared lobules, and proliferation of mesenchymal cells (fibroproliferation) with deposition of extracellular matrix in previously affected lobules (intraalveolar, interstitial, and endovascular), resulting in maladaptive lung repair and ultimately in fibrosis [11]. Recurrent endothelial and epithelial injury leads to protracted vascular permeability ("capillary leak") in the lung and systemically. Intravascular coagulation and fibrocellular intimal proliferation decrease the available pulmonary vascular surface area (pulmonary hypertension and subpleural ischemic necrosis leading to pneumothorax), while intraalveolar fibrin (via systemic inflammation-activated acute-phase response) deposition promotes cell-matrix organization by fibroproliferation [12]. Profibrotic mediators involved in the fibroproliferative response were recently reviewed [13]. High levels of inflammatory cytokines, contrary to low-to-moderate levels, impair neutrophils' phagocytosis and intracellular killing [14] and promote intra- and extracellular growth of nosocomial pathogens, increasing the host's susceptibility to nosocomial infections [15]. Creating a diagnostic challenge to clinicians, (systemic inflammation-associated) fever is common (mostly after the first week of unresolving ARDS) in the absence of an infection.

A GRα-driven response (Table 1) [5]—with decreased (NF-κB driven) release of inflammatory mediators

Table 1 Progression of ARDS: resolving versus unresolving

	Resolving	Unresolving
Onset of ARDS		
Levels of inflammatory cytokines, chemokines, and adhesion molecules[a]	Moderate	Exaggerated
HPA-axis response[b]	Adequate	Inadequate
Over time		
Systemic inflammation	Regulated	Dysregulated
Activation (NF-κB) vs. regulation (GRα) of innate immunity and tissue defense response[c]	GRα-driven	NF-κB-driven
Levels of inflammatory cytokines, chemokines, and adhesion molecules[a]	Decreasing	Persistent elevation
Markers of integrity of the alveolocapillary membrane[d]	Decreasing	Persistent elevation
Levels of fibrogenesis markers[a]	Decreasing	Increasing
Tissue defense response (histology)	Adaptive	Maladaptive
Physiological improvement by day 7[e]	Yes	No
Intensive care unit mortality	Low	High

Modified with permission from Ref. [3]

[a] Plasma and bronchoalveolar lavage: tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, C-reactive protein [5, 19], IL-8, soluble intercellular adhesion molecule-1 [20], procollagen aminoterminal propeptide type I and III [10]

[b] Cortisol: ACTH ratio [5]

[c] Inflammation: systemic (effects of longitudinal plasma samples on normal PBLs) and pulmonary (tissue immunohistochemistry in unresolving ARDS) [5]

[d] Bronchoalveolar lavage total protein, albumin, and neutrophil percentage [19]

[e] Physiological improvement by day 7: reduction in lung injury score ≥1 point or increase in PaO_2:FiO_2 ≥100 [5]

(regulated systemic inflammation) over time—leads to disease resolution [6, 16] with decreased neutrophil recruitment (decreased tissue injury), restoration of the integrity of the ACM (decreased BAL total protein, albumin, and neutrophils), resorption of edema, increased surfactant production, decreased clotting and fibrocellular intimal proliferation with restoration of fibrinolysis (decreased pulmonary hypertension), decreased fibroproliferation and resolution of intraalveolar and interstitial granulation tissue (increased lung compliance, decreased physiologic dead space) [17], neutrophil apoptosis, and switch of proinflammatory (classically activated) into regulatory (alternatively activated) macrophages with elimination of apoptotic inflammatory cells and excess resident tissue cells [16]. Resolution of inflammation and restoration of tissue homeostasis is an active, coordinated process [16] that continues for weeks after removal of assisted breathing.

To conclude, fibroproliferation is an early event in ARDS and an integral component of the NF-κB-activated tissue defense response. Throughout the disease process exudative and fibroproliferative changes coexist with greater prevalence of exudation in early ARDS and fibroproliferation in late ARDS [8]. The fibroproliferative response over time varies quantitatively in response to a reduction vs. an increase in NF-κB activation in circulating and tissue cells [5]. BAL type III procollagen was recently shown to correlate with histological fibroproliferation in unresolving ARDS [18], a potential guide for antifibrotic treatment intervention. Based on the present pathophysiological understanding, however, a treatment intervention initiated in early ARDS and directed at achieving a sustained downregulation of NF-κB should provide the best chance for disease resolution.

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Conflicts of interest Both authors declare no conflicts of interest.

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