The complex role of fibrin in acute lung injury

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IN THE LAST DECADE there have been many advances in our understanding of the pathogenesis of acute lung injury (ALI), but there have been frustratingly few successful therapeutic interventions. In fact, the only treatment proven to reduce mortality is low tidal volume lung-protective mechanical ventilation (1), a non-pharmacological therapy. Furthermore, therapies that have proven successful in related conditions, such as activated protein C (APC) for severe sepsis (6), have been disappointing in patients with ALI (10) despite the fact that activation of coagulation in the lung and local fibrin deposition are central to the pathogenesis of ALI. Why have these treatments failed? The answer may lie in the complexity of the pathogenesis ALI.

In their recent article, Allen et al. (2) report findings from a mouse model of ALI that challenge our current understanding of the role of fibrin deposition in ALI. In this study, the authors use two different transgenic mouse models to reduce fibrin deposition. The first, a fibrinogen-deficient mouse, lacks the necessary precursors to make fibrin polymers (Fgn−/−), and the second has enhanced capacity to degrade fibrin through a deficiency of plasminogen activator inhibitor-1 (PAI-1). Both of these strains have virtually undetectable levels of lung fibrin in response to lung injury compared with wild-type injured mice that have accumulation of lung fibrin. The authors hypothesized that reducing lung fibrin accumulation would be protective in lung injury, a hypothesis that is based on extensive animal and human data suggesting that activation of coagulation and inhibition of fibrinolysis is harmful in ALI. Patients with ALI have disordered fibrin turnover in the air space (8). Baboon studies of sepsis-induced lung injury have shown that inhibition of coagulation through blockade of tissue factor results in attenuated lung injury compared with untreated animals (18, 19). More than a decade ago, Barazzone et al. (4) showed that PAI-1−/− mice exposed to hyperoxia had improved survival compared with wild type. However, these mice had equivalent amounts of vascular leak, and there was no measurement of lung inflammation. Despite the fact that the preponderance of human and animal data suggest that activation of coagulation in the lung is harmful, both Allen and colleagues (2) report that transgenic induction of low levels of fibrin is associated with increased lung inflammatory cell influx and microvascular leak in a model of acid aspiration-induced lung injury. How, then, can we put the results of Allen et al. in context?

Although the earliest pathological studies of ARDS describe extensive hyaline membrane formation (fibrin polymers), the end product of activation of coagulation, there are intermediate enzymes in the coagulation pathway that may be more potent mediators of lung injury. The primary bioactive intermediate in the pathway to fibrin formation is thrombin. Thrombin (factor IIa) is produced as an inactive precursor, prothrombin, that is cleaved and activated by factor Xa. Thrombin is a highly active serine protease that has multiple biological functions in addition to cleavage of fibrinogen to form fibrin. Thrombin exerts many of its biological effects through interactions with protease-activated receptors (PARs). PARs are present on many cell types, including the lung alveolar epithelium (3) and neutrophils (17). Blockade of PAR signaling decreases neutrophil influx in a rat paw inflammation model (7) and in a murine model of systemic inflammation (15). In many cases, effective anti-coagulant therapies are associated with a decrease in thrombin formation. Slofstra et al. (16) showed that inhalation of APC could attenuate LPS-induced lung inflammation and that APC-treated mice had a decrease in thrombin-anti-thrombin complexes in the bronchoalveolar lavage fluid. Furthermore, the few studies that have only modulated fibrin formation without affecting thrombin formation have shown results similar to the work of Allen and colleagues (2). Hyperoxia in PAI-1−/− mice as mentioned above had no effect on lung vascular leak even though fibrin deposition in the lung was reduced. Similarly, in an acid aspiration lung injury model in rabbits, fibrinogen deficiency was associated with increases in lung inflammation compared with animals with normal amounts of fibrin (9). In addition, fibrinogen knockout mice are not protected from bleomycin-induced pulmonary fibrosis despite having undetectable levels of fibrin in the lungs (13). Although Allen et al. did not measure thrombin formation in the current study, neither of the knockout strains would be predicted to have lower levels of thrombin compared with controls. It would be interesting to repeat these experiments in the setting of thrombin inhibition; the findings might be very different. It may be that the proinflammatory effects of thrombin are harmful in the setting of lung injury but that the procoagulant (fibrin polymerization) effects are beneficial, highlighting the complex biological effects of different proteins in the same pathway. The current study by Allen et al. provides critical evidence that there are differential effects of proteins in the coagulation cascade and that these independent effects will need to be studied in great detail before we have a complete understanding of the complex pathogenesis of ALI.

Another important concept that has been increasingly appreciated over the last several years is that modulation of coagulation and fibrinolytic pathways occurs in an organ-specific manner. For years, the prevailing theory held that fibrin formation in the lung happened solely as a consequence of activation of systemic coagulation, with leakage of plasma proteins into the air space accounting for fibrin accumulation. More recent work suggests that while leakage of plasma proteins into the lung is likely an important component of fibrin formation, the resident lung cells actually modulate local coagulation in the air space independent of systemic coagulation. Prabhakaran et al. (14) measured PAI-1 in simultaneous samples of undiluted pulmonary edema fluid and plasma from patients with ARDS and found that levels were significantly higher in the lung fluid, suggesting a local source of PAI-1 in
the lung. There also is local expression of tissue factor, the initiator of the extrinsic coagulation cascade, and the alveolar epithelium is a potential source of coagulation proteins (5). This is critically important when attempts are made to modulate coagulation and fibrinolysis in the lung. Experimental models have demonstrated differential responses to lung injury when treatments were administered directly to the air space compared with systemic treatment. In a sheep model of pneumonia and smoke inhalation-induced lung injury, inhaled heparin significantly attenuated lung vascular leak as measured by wet-to-dry weight ratio, whereas systemic heparin administration had no effect on lung fluid accumulation (12). Other studies have shown that systemic modulation of coagulation does have beneficial effects on the lung. In a rat model of intratracheal LPS, site-inhibited factor VIIa that blocks tissue factor activation resulted in decreased lung inflammation and cytokine levels in the air space (11). These studies raise the important issue that inhibiting a coagulation protease either locally or systemically may have differential effects. Allen et al. (2) used mice that were deficient in PAI-1 or fibrinogen throughout the entire animal. Their findings may have been different if fibrin deposition had been inhibited only in the air space and not systemically. Perhaps the potential beneficial effects of inhibiting fibrin deposition in the lung were offset by the inability to form fibrin polymers in the microvascular space. Maybe pulmonary microvascular fibrin has beneficial effect in the setting of lung injury such as forming a protective barrier and limiting vascular leak. The reverse may also be true with intra-alveolar fibrin deposition protecting the alveolar structure and providing a scaffold upon which to repopulate the epithelium and intravascular fibrin promoting inflammation and vascular leak. The sum of all available data demonstrates that both the specific enzyme being modulated and the location of this intervention are important. Organ-specific modulation of coagulation and fibrinolysis needs further study in animal models of lung injury and will need to be taken into account when designing clinical trials in ALI.

At first glance, the interesting results from Allen et al. (2) may seem to contradict the current body of evidence suggesting an important role for coagulation activation in the lungs during acute injury. A closer look, however, reveals that this study adds important information about the specific, independent roles of coagulation products in disease pathogenesis. Furthermore, it highlights the importance of studying not only systemic modulation of coagulation but also organ-specific regulation of fibrin deposition. This compartmentalization has important implications for treatment of patients with ALI and needs to be addressed when potential therapeutics are being developed. Not only will we need to consider the specific inhibitor (tissue factor pathway inhibitor, APC, hirudin) but we will also need to determine the best route of administration (intravenous, aerosolized) to achieve clinical benefit in patients with ALI. The important and interesting study by Allen et al. adds one more piece to the puzzle of ALI.

GRANTS

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REFERENCES


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