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REVIEW

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ACUTE LUNG INJURY: A CHALLENGING TRANSFER FROM BENCH TO BEDSIDE

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ABSTRACT. ACUTE LUNG INJURY (ALI) and acute respiratory distress syndrome (ARDS) still remain leading causes of death in critically ill patients. Although invaluable insights into the pathophysiology of ALI and the inflammatory process itself have been gained through the use of various animal models during the last decades, bridging the chasm between the bench and the bed is a great challenge, owing to the complexity and variety of clinical conditions associated with these syndromes. Despite promising experimental strategies, therapeutic interventions have been to date largely unsuccessful. Therefore, clinical management of ALI/ARDS patients continues to be a major challenge. In this review, we seek to evaluate the pathophysiology of three commonly used animal models that are employed to mimic ALI/ARDS and analyze the role of the complement system in these models. Moreover, we briefly discuss the problems in the transfer of experimental laboratory data to the clinical setting.

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1. INTRODUCTION

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) were first described by Ashbaugh et al some 30 years ago [1]. Yet today, in spite of tremendous efforts and technical developments in surgical and intensive care units, ALI and ARDS remain a leading cause of death in critically ill patients, affecting 79/100,000 (ALI) [2] and 10–14/100,000 (ARDS) [3] patients annually. Depending on ALI/ARDS definitions, etiology, severity and pre-existing diseases, mortality ranges from 10–90% [2,4-7]. It has been estimated that each year in the US alone there are 190,600 cases of ALI (74,500 with a fatal outcome), and that these are associated with 3.6 million hospital days [2], placing a major burden on the U.S. health system. Both, ALI and ARDS are highly complex polyetiological syndromes [8] that can not only be triggered by various local insults (such as long bone fractures, head injury, lung contusion, blunt chest trauma [9-12], aspiration, near-drowning [13], pneumonia [14-16], lung emboli [17], inhalation of toxic gases [18] or ventilatory damage to the lung [19]), but also by different systemic insults including large volume transfusions and hemolysis [20,21], burn injuries [18], shock, polytrauma [12], the systemic inflammatory response syndrome ("SIRS") and sepsis [22]. Toxic substances like alcohol [23], heroin [24] and paraquat [25] have also been described to induce ALI and/or ARDS. Accordingly, the search for an accurate definition of these syndromes includes more than 50 synonyms, ranging from shock-lung, oxygen pneumonitis to fat embolus syndrome, neurogenic pulmonary edema and ventilator lung. However, since most of these definitions simply describe the relating causative insult, the American-European Consensus Conference sought to simplify the rather confusing terminology in a concerted effort and defined ALI and its fulminant variant, ARDS [22], to allow comparisons between studies. Yet, there is still concern that the parameters used for the proposed measurements do not seem to apply in some clinical settings [26,27].

The clinical features of a patient with ALI/ARDS is characterized by moderate to severe respiratory insufficiency, bilateral thoracic infiltrates on chest films ("snow white lungs") and a reduction of the pulmonary artery wedge pressure (PAOP <18 mmHg). While ALI is additionally defined by an oxygen partial pressure (PaO_2/FIO_2) below 300 mmHg, this pressure falls below 200 mmHg during ARDS [22]. Typically, the pathophysiology of ARDS pursues a three staged pattern. During the first 24–72 hrs patients present with relatively fair symptoms, followed by approximately a one week second phase, which is typified by alveolar edema. Two weeks thereafter, the final stage of proliferation and pulmonary fibrosis begins, leaving ARDS survivors with long-lasting, significant constraints of pulmonary function in every-day activities [28-30]. In this review we seek to evaluate three animal models that are commonly employed to mimic ALI and describe their underlying pathophysiology. Furthermore, we intend to underline the role of complement in ALI/ARDS and briefly elucidate the difficulties, challenges and pitfalls during transfer of information from the bench to the bedside.

2. THE PATHOPHYSIOLOGY OF ALI/ARDS IN RODENT MODELS

2.1. IMMUNE COMPLEX LUNG INJURY

In this widely used model of acute lung injury, immunologic alveolitis is induced in rodents by intrapulmonary deposition of IgG immune complexes. The underlying pathophysiological events have been extensively characterized, but it is still a matter of controversy if this model really represents the situation of ARDS in humans or if it mimics events that occur in human immunological diseases associated with Goodpasture's syndrome, systemic lupus erythematosus, rheumatoid arthritis or immune complex-related glomerulonephritis [31,32]. Following the initial insult, activation of the proinflammatory network results in migration and accumulation of activated neutrophils and activation of lung macrophages. Subsequently, the lung parenchyma is damaged by generation and release of proteases and reactive oxygen and nitrogen species, leading to intrapulmonary hemorrhage and edema

[31]. These reactions require the local activation of complement and the participation of proinflammatory cytokines (TNFα, IL-1), CXC chemokines (MIP-2, CINC, etc) and CC chemokines (MIP-1α, MIP-1β, etc) [33-37]. The production of proinflammatory mediators is regulated by NF-κB, a pluripotent transcription factor which binds to DNA after nuclear translocation during cell activation. Two waves of NF-κB activation have been observed during experimental lung injury: an early peak (30 min) due to activation of NF-κB in lung macrophages and a late increase (4 hrs) involving NF-κB activation in lung endothelial and epithelial cells [38]. The release of cytokines/chemokines and altered surface expression of adhesion molecules on pulmonary endothelial cells leads to the recruitment of neutrophils into the site of inflammation and subsequent oxidant-/protease-mediated tissue injury [39]. In the case of IgG immune complex lung injury, activation of complement plays a central role with its powerful downstream activation product, C5a, being required for the full development of injury (discussed below in detail) [32]. The response is regulated by positive-feedback mechanisms and regulatory factors such as IL-10, IL-13, SLPI (secreted leucocyte protease inhibitor) and SOCS proteins (suppressor of cytokine synthesis) which inhibit NF-κB activation [38,40,41]. The balance between the pro- and the anti-inflammatory cascades determines the intensity and progression of injury. This animal model tends to be the most extensively used to represent the end stage of the injury, perhaps closely mimicing ALI/ARDS including capillary leak, edema and hemorrhage. Much of the ALI/ARDS-pathophysiology known nowadays derives from the use of this model.

2.2. ENDOTOXIN INDUCED LUNG INJURY

Intratracheal administration of lipopolysaccharide (LPS), a component of the cell wall of gram negative bacteria, represents a popular model of acute lung injury in rodents. This model displays key features of microvascular injury as found in patients with ARDS [42]. But in spite of its wide use, the endotoxin model has not yet been comprehensively described and the underlying pathophysiological mechanisms are inadequately understood. The end points of tissue injury (including intrapulmonary leucocyte accumulation, capillary leak and pulmonary edema), are also considered to mimic ARDS and show similarities found in the immune complex model [42]. In general, the same pathophysiological downstream mechanisms as in the IgG-IC model seem to be involved in the LPS model. It has been described that LPS-induced lung injury leads to NF-κB activation and subsequently to production of proinflammatory mediators (TNFα, IL-1, chemokines) which lead to neutrophil transmigration and tissue damage [42,43]. But it is likely that the LPS model of acute lung injury basically and essentially varies from the IgG-IC model in the initiation of the immune response. LPS as a so called pathogen-associated molecular pattern (PAMP) is recognized by toll-like receptors (TLRs) which play an essential role in the innate immune response against infections [44]. TLR4 has a high affinity for LPS and the receptor-ligand interaction triggers the inflammatory process via activation of intracellular signaling pathways (MyD88) followed by NF-κB translocation [44,45]. TLR4 and TRL2 have been reported to be upregulated on bronchial epithelial cells and lung macrophages during LPS-induced ALI [46]. Furthermore, certain other cytokines participate in the regulation of the LPS induced immune response such as macrophage migration inhibitory factor (MIF) and high-mobility group protein (HMG-1), whereas the role of these mediators is not defined in the other models [47,48]. In the case of sepsis, evidence has been presented that LPS-induced inflammation is not a valid model to simulate the sepsis situation, since a completely different profile of cytokine release occurs after LPS administration [49]. So, it remains to be determined whether the findings of LPS induced lung injury really characterize the pathophysiology of ARDS or if they differ in detailed but eventually crucial features.

2.3. BLUNT CHEST TRAUMA

Trauma to the chest still causes approximately 25% of all trauma-induced deaths [50,51]. Several animal models have sought to closely mimic blunt

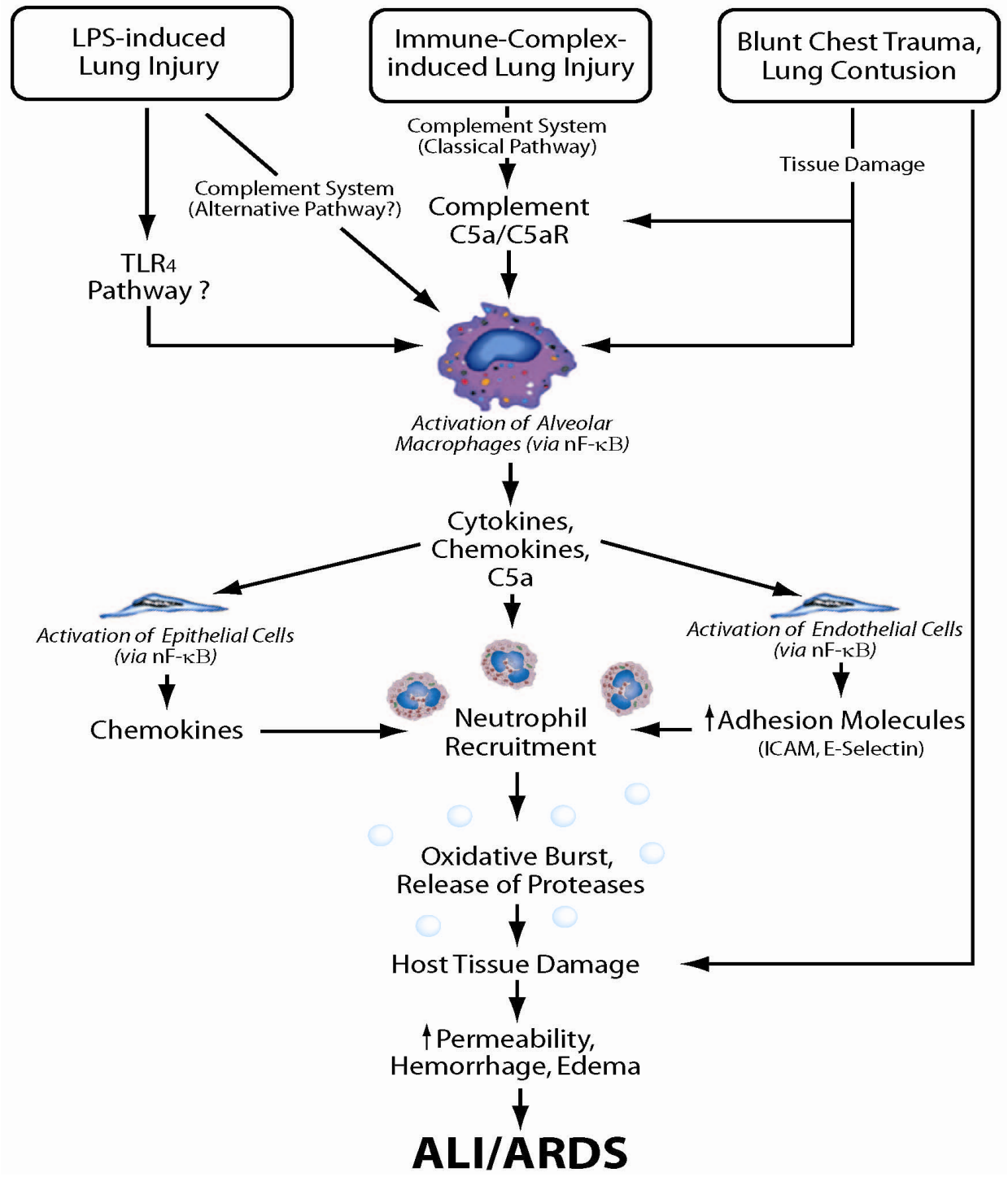

FIGURE 1. PATHOPHYSIOLOGICAL FLOWCHART OF THREE COMMONLY USED ANIMAL MODELS EMPLOYED TO MIMIC ACUTE LUNG INJURY.

chest trauma as it would occur following a motor vehicle accident-induced trauma, blast injury or behind armor blunt trauma (BABT). While some use an actual ballistic impact to cause trauma [52-54], others imitate lung contusion by a blast wave centered on the thorax [55-57]. A recent autopsy-based study provided important insights into the pathophysiology of human blast lung injury [17]. The micromorphological consequences included diffuse alveolar overdistention, interstitial and intrapulmonary hemorrhage, venous air emboli, bone marrow embolism, and massive pulmonary fat embolism. Especially the latter may present a leading risk factor for the rapid respiratory deterioration with progressive hypoxia developing in blast victims who survive the initial impact. Interestingly, the authors concluded that the embolism did not seem to be a mere ventilation-induced artifact, but rather a uniform pathophysiological finding following blast injury. The inflammatory response subsequent to lung contusion is characterized by the following path (see FIG. 1): Traumatic chest wall impaction causes lung contusion when force is transmitted to lungs [58]. The resulting damage to lung tissue and rupture of airways have been reported to activate alveolar macrophages and the complement system [59,60]. Upon activation, alveolar macrophages unleash their major arsenal of proinflammatory mediators [55,61-63], complement activation products [64] and cellular proteases [60], cleaving complement factor C5 to generate the powerful anaphylatoxin fragment, C5a [65]. C5a leads to robust recruitment and influx of additional phagocytes into lungs, resulting in further host tissue damage, culminating in a explosive inflammatory end-stage [8,59,60]. The resulting functional and morphological changes ultimately lead to pulmonary edema, respiratory distress [66], ALI, and ARDS. There is increasing evidence from clinical studies that levels of C3a and C5a in patients at risk for ARDS are elevated [67-69], suggesting a role for complement activation products in the pathophysiology of ALI/ARDS (discussed below).

3. ROLE OF COMPLEMENT IN ALI

The complement system as a part of innate immunity plays a central role in the containment or progression of various infectious and non-infectious diseases. Besides eradicating invading micro-organisms by assembly of the membrane attack complex, products of complement activation can induce the production of endothelial adhesion molecules, the release of oxygen radicals and the expression of cytokines/chemokines and can act as a direct chemoattractant to neutrophils [70]. Most complement proteins can be produced in the lung by either type II pneumocytes, alveolar macrophages or lung fibroblasts [71-73]. Some time ago, several studies reported significant intrapulmonary activation of complement in patients with ARDS which even seemed to be related to the development and outcome of disease [67,68,74,75].

Immune complexes are potent activators of the classical pathway of the complement system. C5a has been demonstrated to be required for the full development of lung injury in the IgG-IC model [32,59]. Following IgG-IC deposition complement activation appears to be an upstream event in the inflammatory response, enhancing the production of early response cytokines (TNFα and IL-1). Therefore, C5a as well as the membrane attack complex act synergistically with a co-stimulus (IgG-IC) to intensify the inflammatory response and tissue injury [76]. Blockade of C5a by concomitant administration of anti-C5a IgG at the time of IgG-IC deposition greatly diminished tissue injury represented by a reduced capillary leak and neutrophil influx. This protective effects of anti-C5a were associated with reductions of TNFα, CC- and CXC chemokines levels in BAL fluids and with decreased endothelial ICAM-1 upregulation indicating a key role for C5a in the initiation of the inflammatory network [32; 77]. The cellular effects of C5a are mainly mediated via C5aR, a specific 7-transmembrane rhodopsin-type receptor, which activates the intracellular MAP-Kinase cascade after ligand binding to C5aR and G-protein engagement [78]. Subsequently, NF-κB is translocated to the cell nucleus and above described alterations in cell activity occur.

In contrast, the role of complement in LPS induced ALI is poorly understood. It was suggested a long time ago that depletion of complement did not

prevent the increase of pulmonary capillary leak induced by LPS [79]. When human lung type II pneumocytes were exposed to LPS *in vitro*, C3 levels increased, but LPS had no effect on C5 production [73]. Thus, it is not clear to what extent complement activation, and especially C5a generation, may play a role in the development of lung injury in the LPS model, even though LPS is known to be an activator of the alternative pathway of the complement cascade. The decisive events in LPS induced inflammatory responses seem to be TLR4 dependent. A recent publication suggests that C5a negatively regulates TLR4 expression on macrophages so that mutual cross-talks between the two systems could be assumed [80].

Very little is known about the participation of complement in the development of trauma related ARDS. According to our own findings, there is extensive activation of the complement system only minutes after injury (pending publication). Moreover, C5a seems to play a key role in modulating the innate immune response following blunt chest trauma (pending publication). But when exactly and under which circumstances does the complement system turn from friend to foe? Under what conditions and pre-existing co-morbidities do the lungs get involved? Via which pathways do head injury, burn injuries and hemolysis trigger ALI/ARDS?

4. THE CHALLENGE FROM BENCH TO BEDSIDE

Despite tremendous efforts to comprehend the pathophysiology of ARDS in experimental studies, the actual pathophysiologic changes in patients with ARDS are stillpoorly understood and further investigation is required to further complete the mysterious mosaic of ALI/ARDS. As already mentioned, activation of complement is associated with the development of ARDS in humans [67,68,74,75]. Two clinical studies confirmed increased NF-κB activation in alveolar macrophages in patients with ARDS [81,82]. In addition, elevated levels of cytokines/chemokines and adhesion molecules have been described in BAL fluids and serum during ARDS in humans, inducing activation of macrophages and sequestration of neutrophils [83,84]. Some of these mediators (TNFα, IL-1, sVCAM-1, sICAM-1; IL-6, IL-8, IL10) seem to correlate with the clinical outcome [83,85] and might be used as potential markers for the diagnosis and prognosis of ARDS.

A proficient treatment for ALI and ARDS is still a remote dream for clinicians. Bridging the chasm between bench and bedside seems especially challenging. During recent years, research on therapy has mainly focused on both mechanical ventilation strategies and pharmacological interventions. Animal and human clinical studies have demonstrated the role of certain types of mechanical ventilation in perpetuating lung injury [86], leading to macroscopic damage, diffuse ventilator-induced lung injury and multiple-organ failure [87,88]. However, a large clinical study was stopped early after an interim analysis after a significant reduction of mortality in the group receiving low compared to traditional tidal volumes was found [89]. The diversity of approaches to pharmacologic therapy for ALI/ARDS equals the complex pathophysiology. Agents that have appeared promising in experimental and early clinical studies have failed in large randomized clinical trials. Trials included corticosteroids and various other anti-inflammatory agents, pulmonary vasodilators and surfactants. There were many trials studying the effects of PGE1 [90-96], N-acetylcysteine [97-101], high- and low-dose corticosteroids [102-104], and surfactants [105-108] on ALI/ARDS. Disappointingly, all of these studies showed none or only mild, non-significant results. Some of the interventions even had to be discontinued due to adverse events. In addition, given the serious concern about increasing the risk of nosocomial infections by administration of high-dose glucocorticoids to critically ill patients, routine use of corticoids cannot be recommended at present [109,110]. Disappointingly, no pharmacotherapy convincingly improved survival in ALI/ARDS patients so far. This might be due to the enormous heterogeneity of patients enrolled in these studies. As more and more data become available about the molecular profiling and individual risk factors for ALI/ARDS (see ref. [111] for a concise review), it seems that

ALI/ARDS cannot be treated with a sole "magic bullet", but rather needs to be evaluated on a very individual basis, taking the personal etiology, risk factors and genomic predispositions of each patient into account.

Therefore, the clinician is left with very few options aside from standard support measures. First and foremost, the underlying cause (e.g. pneumonia, sepsis) of ALI/ARDS needs to be identified in order to take appropriate therapeutic approaches. There is still a large amount of uncertainty about the management of the volume status, hemodynamics and the appropriate nutrition in ALI/ARDS patients. The only supportive therapy that has been shown to reduce mortality in ALI/ARDS so far is low tidal volume ventilation [89].

Despite the dismal findings in the numerous pharmacological studies cited above, new therapeutic strategies are under investigation. In a very new clinical trial, salbutamol has been shown to reduce lung water and plateau airway pressure [112]. One of the potential key areas that have been largely neglected in the therapeutic realm is a selective, patient-and stage-adjusted, individual modulation of the inflammatory response. Moreover, there is now increasing evidence of an extensive cross-talk between the innate immune and the coagulation system (see ref. [113] for a review). Given the fact that, very much like sepsis, ALI/ARDS occurs as a procoagulant, anti-fibrinolytic state [114-116], specific modulation of either innate immunity or the coagulation system might put new hope on the horizon [117], as mortality has been shown to be reduced by administration of recombinant activated protein C in sepsis [118].

5. CONCLUSION

The terms ARDS and ALI comprise a huge variety of causes of acute respiratory failure and are still insufficiently defined in ways that can lead to more efficient therapeutic interventions. So, numerous experimental models have been developed to simulate some of the diverse pathologic mechanisms. But due to the heterogeneity and complexity of ARDS, none of the experimental approaches can be claimed as the ideal model. All of them use one particular trigger to induce pulmonary injury and do not address other relevant conditions like underlying diseases which might promote the development of ARDS. This makes it difficult to transfer experimentally obtained data to an individual clinical situation. Nevertheless, findings in experimental models are essential to get better understandings of the molecular events behind acute lung injury. With the awareness of the limits of the investigated model, new findings need to be confirmed in patients with ARDS before they can be used as markers or even therapeutic targets. In future, new markers could help to establish a staging system for ARDS (as it is currently being attempted with the PIRO system for sepsis [119]). Including the cause of ARDS, the immunophenotype and predisposition of the patient and other factors, such a system should be able to distinguish between the different forms and stages of ARDS in order to manipulate the inflammatory response with selective therapeutics depending on the individual immune status and point of disease. Future experimental studies need to evaluate these molecular and genetic mechanisms of ARDS more in detail, especially because the different complex inflammatory and coagulatory networks involved in ARDS appear to be closely connected with each other.

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