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Molecular strategy for alveolar protection in severe ARDS

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The systemic inflammatory response syndrome (SIRS) develops in conditions of surgery, trauma, pancreatitis, and infection [1]. It can lead to multiple organ failure, especially in a second hit of infectious bacterial complication [2]. Acute respiratory distress syndrome (ARDS), a severe form of acute lung injury (ALI), is often induced in patients with SIRS. Many recent experimental research studies and randomized clinical trials have described therapeutic strategies for ALI/ARDS [3], but the mortality continues to exceed 40%, especially in severe ARDS with $Pa_{O_2}/F_{I_{O_2}}$ less than 80 mmHg. Thus, it is important to prevent the progression of ALI/ARDS to severe ARDS.

One of the characteristics of ALI/ARDS is that vascular endothelial permeability and coagulopathy are enhanced in the lung. The increased permeability and coagulation can be induced by proinflammatory molecules, including inducible nitric oxyde synthase (iNOS), cyclooxygenase 2 (COX2), and tissue factor, which are upregulated by the activation of nuclear factor κB (NF-κB). In normal cells, NF-κB is present as a latent cytoplasmic complex bound to its inhibitor protein, I-κB. In ALI/ARDS, NF-κB is activated via the intracellular signaling of Toll-like receptor, interleukin receptor, and tumor necrosis factor (TNF) receptor, dissociates from I-κB, and translocates to the nucleus, where it produces proinflammatory molecules, as shown in Table 1. Recently, our studies demonstrated that the inhibition of NF-κB activation using decoy oligodeoxynucleotides (ODNs) reduced expression of the proinflammatory molecules in septic mouse lungs. The in vivo transfer of NF-κB decoy ODNs can inhibit overexpression of the molecules involved in vascular leakage in septic mice [4]. Thus, activation of NF-κB results in enhancement of vascular permeability or microvascular coagulopathy in ALI/ARDS.

However, epithelial injury in alveoli and the microvasculature were identified in the lungs of patients who died of severe ARDS. Alveolar epithelial cells often become detached from the basement membrane by necrosis and apoptosis in severe ARDS. Once the alveolar epithelium is damaged, epithelial permeability leads to strong alveolar flooding with high-molecular-weight proteins such as albumin, with structural repair being prolonged in the alveoli. Epithelial cell death occurs in two general ways, necrosis and apoptosis, which may be different from the effect of NF-κB activation in the lung.

One of the cell-death mechanisms, necrosis, is nonselectively induced in many types of cells in the lung by oxygen radicals, bacterial exotoxins and direct disruption of mechanical ventilation, which may affect the fundamental severity of ALI/ARDS, in addition to inflammation caused by NF-κB activation. On the other hand, apoptosis' another form of cell death, can either ameliorate or exacerbate ALI/ARDS, depending on the cell types involved. The lung contains many differ-

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Table 1. Inflammatory molecules induced by NF-κB activation

Proinflammatory cytokines
Tumor necrosis factor α
Interleukin-1β
Interleukin-2
Interleukin-6
Granulucyte colony-stimulating factor
Macrophage colony-stimulating factor
Chemokines
Interleukin-8
Macrophage inflammatory protein 1α
Macrophage chemotactic protein 1
Eotaxin
Gro-α, -β, -γ
ENA–78
Inflammatory enzymes
Inducible nitric oxide synthase
Inducible cyclooxygenase-2
5-Lipoxygenase
Cytosolic phospholipase A2
Adhesion molecules
Intracellular adhesion molecule-1
Vascular cell adhesion molecule-1
E-selectin
Coagulation
Tissue factor
Plasminogen activator inhibitor-1

ent types of cells, including epithelial cells, endothelial cells, infiltrating inflammatory cells, and fibroblasts. It has been suggested that the apoptosis of polymorphonuclear (PMN) leukocytes can blunt inflammation in ALI/ARDS, but the apoptosis of alveolar epithelial cells (AECs) may be fatal in the management of ALI/ARDS.

There are two distinct types of AECs (AEC1 and AEC2) in the alveolus; AEC1 transports oxygen and carbon dioxide across the alveolar space to the capillary beds that surround the alveoli. AEC1 is terminally differentiated and, therefore, incapable of cell differentiation in ALI/ARDS, while AEC2 retains the ability to promote proliferation by itself, unlike AEC1 [5]. Moreover, AEC2 contains prominent cytoplasmic lamellar bodies and is able to perform surfactant synthesis and secretion. As AEC2 can also differentiate into AEC1, it is very important, for the conservation of alveoli in ALI/ARDS, to prevent the apoptosis of AEC2.

Our new finding, using an experimental model of sepsis, showed that the mRNA expression of molecules of

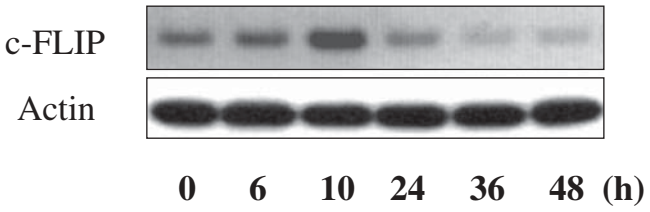

Fig. 1. Western blot analysis of FLICE-inhibitory protein, c-FLIP, in lungs from mice that were sham-operated, 6 h, 10 h, 24 h, 36 h, and 48 h after cecum ligation and puncture (CLP). Actin was unaffected by CLP

the death receptor family, such as TNF receptor 1, FAS, DR4, and DR5 in mouse lungs was increased by three to fivefold 24 h after cecum ligation and puncture (CLP). Moreover, FLICE-inhibitory protein, c-FLIP, was increased in mouse lungs 10 h after CLP, but was reduced by about 36% in sham-operated control lung 24 h after CLP, as shown in the Fig. 1. As a result, we confirmed that apoptosis was strictly associated with the activation of death receptors and FLICE (caspase 8) in the lung in septic ALI/ARDS.

It is well known that critically ill patients with ARDS tend to be healed as pulmonary fibrosis develops after AEC death. In conclusion, anti-apoptotic therapy with AEC2 may be useful for managing severe ARDS successfully and for alveolus reconstitution. Anti-apoptotic gene therapy targeting AEC2 is expected in future.

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