Interleukin-8 and Adult Respiratory Distress Syndrome

The adult respiratory distress syndrome (ARDS), a process of diffuse inflammation and increased permeability of pulmonary microvasculature, carries a high morbidity and mortality (40–90%) (1). Neutrophils have received a great deal of attention as the primary effector cells of this disease process. There is a marked increase in the number of neutrophils in the alveolar spaces. High concentrations of neutrophil elastase and myeloperoxidase are found in bronchoalveolar lavage fluid (BALF) of patients with ARDS. Moreover, there is considerable evidence linking neutrophils and the severity of ARDS (2). In addition, many animal models of ARDS are totally or partially dependent on the presence of neutrophils (3).

Cytokines are endogenously produced small proteins that possess multiple biologic activities, even in low concentrations. Cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1) induce local as well as systemic inflammatory responses through generalized endothelial cell activation. TNF and IL-1 are potent inducers of IL-8 synthesis from macrophages, fibroblasts and endothelial cells. These cytokines are suspected to be responsible for systemic inflammatory response syndrome and multiple organ failure (4). Hence, TNF, IL-1, and IL-8 are grouped together and termed "proinflammatory cytokines".

IL-8 is a chemotactic peptide that is important in local inflammation like pneumonia and ARDS (5). IL-8 attracts neutrophils to pass from the circulation to tissues. Furthermore, IL-8 activates neutrophils to release their enzymes and to generate reactive oxygen species, which break down tissues. The endothelium becomes leaky after exposure to IL-8-activated neutrophils and results in permeability edema and organ dysfunction.

The hypothesis that IL-8 is the key mediator of ARDS is attractive. Ikuta et al demonstrated in this issue that ARDS patients with sustained high levels of circulating IL-8 have a poor prognosis (6). We have also observed that IL-8 concentrations in BALF or pulmonary edema fluid are correlated with lung neutrophil accumulation and the degree of lung injury in various clinical settings (7–9). Measurement of IL-8 in patients with ARDS may enable us to monitor the disease activity and, therefore, to assess the effect of future pharmacological interventions.

In 1980, Hammerschmidt et al reported that the presence of a leukocyte aggregant, C5a, in plasma predicted the subsequent onset of ARDS (10). They hypothesized that all risk factors for ARDS, such as endotoxemia, trauma, and pancreatitis, have the ability to activate intravascular complement which could induce intrapulmonary neutrophil aggregation and neutrophil-mediated lung injury, or ARDS. This hypothesis seemed to establish the definitive mechanisms of ARDS, but studies conducted to confirm this hypothesis failed to do so. Now it is thought that the complement component has no reliable predictive value for recognizing patients with ARDS.

Currently, there is no single marker to predict the onset, severity or outcome of ARDS. It seems unlikely that only one mediator plays the central role of the complicated network of cytokines and cellular interactions in ARDS. The measurements of the key mediator, however, may help to understand the mechanisms in this fatal disorder. It is also possible that some marker has a predictive value in certain specific clinical conditions. IL-8 may be the likeliest candidate. Until larger prospective studies resolve this issue the conclusion is pending.

Minoru Kanazawa, MD
Department of Medicine, School of Medicine, Keio University, 35 Shinonomachi, Shinjuku-ku, Tokyo 160

References
