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JA SYMPOSIUM

Acute lung injury and alveolar epithelial function

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Acute lung injury (ALI) or its severe form, acute respiratory distress syndrome (ARDS), is one of the common causes of acute respiratory failure. Although critical care management has improved in recent decades, the mortality rate remains high. Its diagnosis is clinically defined as hypoxemia, bilateral infiltrates on chest radiograph, and exclusion of left atrial hypertension [1]; thus, impaired oxygenation has been considered as a main feature of ALI. Therefore, our research was focused on improvement in oxygenation at the very beginning, and we studied rescue oxygenation treatments such as nitric oxide inhalation and partial liquid ventilation. However, pathological changes in ALI/ARDS consist of multiple aspects, such as activation of inflammatory cells and damage to epithelial cells and endothelial cells. Therefore, treatment strategies should be targeted to the repair of damaged lung tissues and restoration of physiological functions, which could finally result in improvement of oxygenation.

Alveolar epithelial dysfunction is one of the main features in the pathophysiology of ALI/ARDS

Recently, our research activity has been focused on the epithelial function in acute lung injury. Alveolar epithelial cells have several important functions, including maintaining a tight barrier, regulating surfactant production, and removing excess alveolar fluid by vectorial ion transport. Among them, alveolar fluid clearance (AFC) is a key function for prevention of alveolar edema, and its impairment results in the poor prognosis of patients with ALI/ARDS. Ware et al. [2] measured AFC by measuring protein concentration of alveolar edema fluid sampled from patients with ARDS, and patients with AFC <14%/h had significantly higher mortality compared with those with AFC >14%/h. In this sense, measurement of AFC could be a useful approach to evaluate patient severity; however, it is still uncommon in clinical practice because of the methodological difficulty.

Evaluation of alveolar epithelial dysfunction using biomarkers

To overcome this problem, our group chose a strategy to use biomarkers to evaluate epithelial function. In general, tissue-specific proteins that are released into the blood are

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used as tissue-specific biomarker proteins. There are two phenotypes in alveolar epithelial cells: type I and type II epithelial cells. Type I epithelial cells cover 95% of the alveolar surface area, and they might contribute to AFC as well as maintaining barrier function, whereas type II cells have important functions including AFC and production of alveolar surfactant. Although several biomarkers have already been developed with excellent performance to detect type II epithelial cell injury, there were few for type I epithelial cells. Therefore, we studied a candidate biomarker for type I alveolar epithelial cell injury, the receptor for advanced glycation end products (RAGE). RAGE is a cell-surface protein that belongs to the immunoglobulin superfamily, and its expression is most abundant in the lung [3]. In the lung, RAGE is expressed on the basal membranes of type I alveolar epithelial cells [4]. Animal studies demonstrated that RAGE was dose dependently released into the bronchoalveolar lavage fluid and serum, both in an acid aspiration lung injury model and in a lipopolysaccharide-induced lung injury model [5]. In human studies, the RAGE levels were higher in the plasma and the alveolar edema fluid of patients with ARDS than those from patients with hydrostatic pulmonary edema [5]. Also, a study using an isolated perfused human lung model showed that the RAGE level in the alveolar fluid was positively correlated with the RAGE level in the perfusate, and the RAGE level in the alveolar fluid was negatively correlated with AFC [6]. In vitro study using the rat alveolar epithelial cell culture model demonstrated that RAGE was released from alveolar epithelial cells via a shedding mechanism by proteases including matrix metalloproteinase-13 [7]. Therefore, we hypothesize that RAGE might be released from alveolar epithelial cells in the human lung by a proteolytic mechanism caused by proteases induced by inflammatory reactions.

Clinical studies for RAGE as a biomarker of type I alveolar epithelial injury

Recently, several reports demonstrated the clinical results of RAGE measurements. Calfee et al. measured RAGE levels in the 676 patients enrolled in the ARDS Network randomized controlled trial of 6 ml/kg versus 12 ml/kg ventilation. They demonstrated a positive correlation of RAGE level with their lung injury score, and a higher baseline RAGE level was associated with increased mortality and fewer ventilator-free and organ failure-free days in patients randomized to higher tidal volume [8]. Furthermore, Christie et al. studied 317 patients with or without primary graft dysfunction (PGD), defined as bilateral diffuse infiltrate in the chest X-ray and $PaO_2/FIO_2 < 200$ mmHg, after lung transplantation. They demonstrated that patients who developed PGD had higher levels of RAGE than patients without PGD at both 6 h and at 24 h post transplantation [9]. Also, a multicenter study of perioperative RAGE level in patients with cardiac surgery has been recently undertaken in our country. Preliminary results of this study demonstrated that RAGE levels were elevated immediately after the operation using cardiopulmonary bypass, and then decreased by 3 days after the operation. Furthermore, postoperative RAGE levels were significantly correlated with the duration of stay in the intensive care unit and with the duration of mechanical ventilation, whereas neither serum surfactant protein-D nor plasma von Willebrand factor demonstrated significant correlation with those prognostic parameters.

Future perspectives

So far, RAGE is a useful biomarker for type I alveolar epithelial injury, which might reflect severity of the damage in the lung at the point of insult. In future, biomarkers for alveolar epithelial injury might help selecting an appropriate cohort of patients for treatments targeted to improve alveolar epithelial function. In this sense, profiling of multiple biomarkers in patients with ALI/ARDS might be important for decision making in future therapeutic strategies, as well as for developing new treatments for restoration of tissue-specific functions.

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