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Translational studies in the ex vivo human lung



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## Editorial

# Translational studies in the *ex vivo* human lung

Over two decades, considerable progress has been made in the basic and clinical research of alveolar fluid clearance under normal and pathological conditions using the *ex vivo* human lung model. Alveolar fluid clearance describes the function of alveolar epithelial cells to remove alveolar fluid from the alveolar space across the alveolar epithelial barrier. In hydrostatic pulmonary edema, as well as in acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), alveolar fluid clearance drives the resolution of pulmonary edema. Although there are several experimental preparations in animals and in *in vitro* models to elucidate the mechanisms responsible for alveolar fluid clearance, an experimental model using the *ex vivo* human lung is valuable for assessment prior to clinical trials for lung diseases. The human lung preparation was originally designed by thoracic surgeons in Sendai Kosei Hospital and Tohoku University, Japan, in collaboration with Dr. Matthay in University of California, San Francisco [1].

Prior to the development of *ex vivo* human lung model, an analysis of serial samples of distal bronchial edema fluid from patients with pulmonary edema demonstrated the role of active transport in the resolution of alveolar edema fluid for the first time [2]. However, it was difficult to test the effect of agents on the rate of alveolar fluid clearance in the clinical setting. In addition, another unresolved issue was the species differences in the effect of beta-adrenergic agonists that would be a candidate of therapy for accelerating the resolution of pulmonary edema in patients.

Because of the results of an experimental study that alveolar fluid clearance occurred in the absence of any pulmonary perfusion, the *ex vivo* human lung preparation was designed in the excised human lungs from patients with lung cancer [2]. The preparation demonstrated new findings. Alveolar fluid clearance in the human lung depends on amiloride-sensitive sodium channel and ouabain-sensitive Na-K ATPase, components of active ion transport in the *ex vivo* human lung. Terbutaline, a beta-adrenergic agonist, stimulated alveolar fluid clearance *via* the adrenergic receptor and the sodium channel. Although the basic mechanisms responsible for alveolar fluid clearance were determined in the *ex vivo* human lung, there were limitations because of the absence of pulmonary perfusion.

Since the worldwide low utilization of potential donor lungs is persistent, the capability of alveolar fluid clearance in the donor lungs rejected for lung transplantation was used to assess the rejected donor lungs [3]. Then, Frank et al. developed a new human lung preparation with pulmonary perfusion. Lungs from brain-dead organ donors that were rejected for lung transplantation were provided by the Northern California Transplant Donor Network [4]. The study indicated that pulmonary perfusion improved the rate of alveolar fluid clearance in the human lung and the possibility to deliver test substances and therapeutic agents through the vasculature.

Recently, cell therapy using human mesenchymal stem cells (MSCs) has become a promising candidate for acute lung diseases, particularly for ALI/ARDS. Lee et al. used the *ex vivo* human lung preparation and demonstrated that treatment with allogeneic bone marrow-derived human MSCs improved lung endothelial barrier permeability and restored alveolar fluid clearance [5,6]. Interestingly, there are cell contact-dependent and independent mechanisms in the treatment of MSCs that suggest the capability of rescue in both injured pulmonary endothelium and alveolar epithelium [7].

There is only one effective to reduce mortality for ARDS, low tidal volume lung protective ventilation [8]. Thus, new treatments are needed. The current National Heart, Lung and Blood Institute (NHLBI) portfolio has focused in part on basic research to build fundamental knowledge of the role of stem/progenitor cells in lung disease and injury/repair [9]. As translational work progresses to assess efficacy and safety, studies in the *ex vivo* human lung can play an important role in the basic science studies and the preclinical work for clinical trials, and will continue to be needed more to test efficacy and safety of new treatments.

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