J Anesth (2007) 21:120–121
DOI 10.1007/s00540-006-0474-x

Journal of Anesthesia

Prophylactic and therapeutic approaches to acute lung injury, targeting alveolar epithelial type II cells

Katsuya Mikawa, Kahoru Nishina, Takuyo Misumi, Toshihiro Ando, and Hidefumi Obara

Department of Anesthesia and Perioperative Medicine, Kobe University Graduate School of Medicine, 7 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

K. Mikawa

Alveolar epithelial type II cells (AEC-II) play an important role in the repair of alveolar epithelium because of their differentiation into alveolar epithelial type I cells (AEC-I). In acute lung injury (ALI), various inflammatory mediators produced in the lung attack AEC-II, leading to extensive loss of the alveolar epithelium. We discuss potential therapeutic approaches to ALI, targeting AEC-II. The basic concept of our strategy lies in the restoration of the quantity and function of AEC-II. Several growth factors (e.g., keratinocyte growth factor [KGF], and hepatocyte growth factor [HGF]) are known to potentiate AEC-II proliferation in both in vitro and in vivo systems. However, the clinical application of the growth factors does not seem feasible, because of their high cost. As an alternative to the administration of these agents, therefore, adenovirus-mediated *KGF* gene transfer into AEC-II has been attempted experimentally, with success [1]. For the same purpose, we have sought a simple pharmacological modality by which AEC-II proliferation could be accelerated, and have found that rolipram, a phosphodiesterase (PDE)-IV inhibitor, enhanced the growth of cultured AEC-II without influence on fibroblasts [2]. The enhancing effects of rolipram and KGF/HGF were additive. Further studies are required to confirm the clinical efficacy of the drug in enhancing AEC-II proliferation. However, because pulmonary fibrosis is the main cause of death in the late phase of ALI, it is important to prevent fibrotic changes of the lung in response to various insults by inhibiting fibloblast proliferation. Of interest is the observation that culture of lung fibroblasts in the presence of AEC-II can minimize fibroblasts growth through a mechanism mediated by prostaglandin E2. In the progress of ALI, the apoptosis of AEC-II contributes to extensive destruction of the alveolar epithelial architecture. Therefore, we assessed the effects of various drugs that are often used perioperatively on the endotoxin-induced apoptosis of cultured primary rat AEC-II. We observed that a clinically relevant concentration of propofol inhibited AEC-II apoptosis. Rolipram also had this action. The acid-base balance condition of the culture medium is thought to influence AEC-II apoptosis. In our experiment using cultured A549 cells, an AEC-II-like cell line, hypocapnic alkalosis potentiated the hydrogen peroxide-induced apoptosis of A549 cells and caspase activation, although an acidified medium did not change the oxidative-induced apoptosis of the A549 cells. Anesthetists have recently focused much attention on ventilatory management to prevent the exacerbation of lung damage in ALI. In several animal experiments, hypocapnic alkalosis has been recognized to worsen ALI induced by reactive oxygen species (ROS). Thus, the enhancement of AEC-II apoptosis by hypocapnic alkalosis may be responsible for hyperventilation-induced deterioration in ALI. Another plausible therapeutic strategy for ALI is to prevent the suicide of AEC-II. We must emphasize that AEC-II, as well as being victims in the pathogenesis of ALI, also act as attackers. In response to various

Address correspondence to: K. Mikawa
Received: October 10, 2006

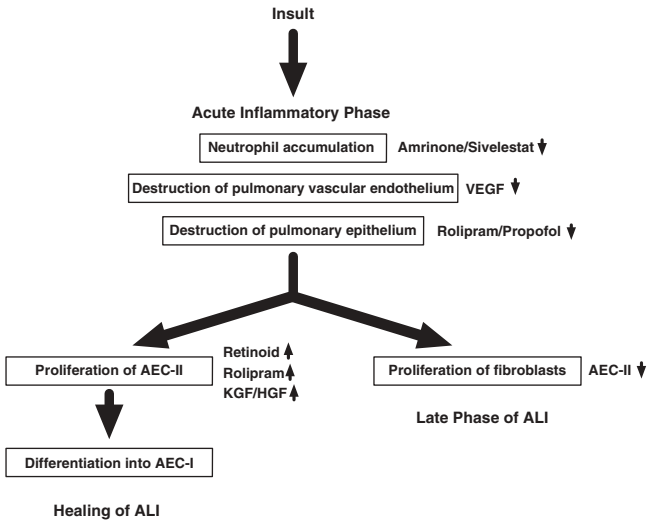

Fig. 1. Potential prophylactic/therapeutic strategies for acute lung injury (*ALI*) targeting alveolar epithelial type II cells (*AEC-II*). *VEGF*, vascular epithelial growth factor; *KGF*, keratinocyte growth factor; *HGF*, hepatocyte growth factor; ↑, enhancenment; ↓, attenuation

stimulants, AEC-II have the ability to produce many inflammatory mediators which participate in the manifestation and progression of ALI. We have found that amrinone, a PDE-III inhibitor, downregulated the production of interleukin-8 and monocyte chemoattractant protein-1 by A549 cells at the transcriptional level [3]. Sivelestat (an elastase inhibitor) also had this action. Regulation of the biosynthesis of these chemokines in AEC-II with amrinone or sivelestat may have an important impact on the immunoresponse of the cells in inflammatory conditions in the lung. Figure 1 summarizes potential prophylactic/therapeutic modalities for ALI from the viewpoint of targeting AEC-II. Our final goal is the establishment of pulmonary regeneration as a reliable therapy for ALI. From the results of several series of our experiments using AEC-II, we believe that the promotion of epithelial regeneration is the first step in promising therapeutic approaches to ALI, and that this regeneration provides a clue to success in lung regeneration.

References

1. Morikawa O, Walker TA, Nielsen LD, Pan T, Cook JL, Mason RJ (2000) Effect of adenovector-mediated gene transfer of keratinocyte growth factor on the proliferation of alveolar type II cells in vitro and in vivo. Am J Respir Cell Mol Biol 23:626–635
2. Nishina K, Mikawa K, Morikawa O, Obara H, Mason RJ (2002) The effects of intravenous anesthetics and lidocaine on proliferation of cultured type II pneumocytes and lung fibroblasts. Anesth Analg 94:385–388
3. Misumi T, Tanaka T, Mikawa K, Nishina K, Morikawa O, Obara H (2006) Effects of sivelestat, a new elastase inhibitor, on IL-8 and MCP-1 production from stimulated human alveolar epithelial type II cells. J Anesth 20:159–165