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Review:

Organ preconditioning: the past, current status, and related lung studies

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Abstract: Preconditioning (PC) has emerged as a powerful method for experimentally and clinically attenuating various types of organ injuries. In this paper related clinical and basic research issues on organ preconditioning issues were systemically reviewed. Since lung injuries, including ischemia-reperfusion and others, play important roles in many clinical results, including thromboembolism, trauma, thermal injury, hypovolemic and endotoxin shock, reimplantation response after organ transplantation, and many respiratory diseases in critical care. It is of interest to uncover methods, including the PCs, to protect the lung from the above injuries. However, related studies on pulmonary PC are relatively rare and still being developed, so we will review previous literature on experimental and clinical studies on pulmonary PC in the following paragraphs.

Key words: Preconditioning, Ischemia-reperfusion, Lung
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PRECONDITIONING: AN OVERVIEW OF VARIOUS ORGANS

Preconditioning (PC) is a process where cells or tissues exposed to a sublethal stimulus are transiently protected from a subsequent normal lethal stress (Nandagopal *et al*., 2001; Cutrn *et al*., 2002; Kirino *et al*., 1991; Kirino, 2002; Raeburn *et al*., 2001; Peralta *et al*., 1999; Gasparri *et al*., 1999). Many forms of preconditioning have been investigated, such as ischemic, thermal, pharmacologic, or gas inhalation (particularly in lung injury) (McCormick *et al*., 2003). Preconditioning can attenuate the subsequent prolonged or lethal tissue injury by increasing the cell tolerance to the stress.

Organ PC was first recognized by Murry *et al*.(1986), who originally tried to create a larger area of myocardial infarction by performing several brief episodes of myocardial ischemia prior to protracted ischemia, but got paradoxical results. The protective effect of PC in the heart can be assessed by limiting infarct size, reducing myocardial stunning, preventing arrhythmias, or accelerating the recovery of myocardial function after ischemia (Muller *et al*., 1990; Tamura *et al*., 1997; Cleveland *et al*., 1996; Sun *et al*., 1995; Shiki and Hearse, 1987; Pomerantz *et al*., 2000).

Organ PC plays a very important role in the pathogenesis and treatment of cardiac disease (Kuzuya *et al*., 1993). The heart possesses a remarkable ability to adapt to stress and is resistant to injury. The recognition of PC in myocardium has been one of the major advances in the field of myocardial ischemia. In addition to the protective effects of PC on ischemic myocardium, PC can also be found in patients undergoing open heart surgery with cardiopulmonary bypass (CPB) (Li *et al*., 1998a; 2001). Patients undergoing repeated cycles of aortic clamping ischemia for 3 min followed by 2 to 3 min of reperfusion prior to cardiopulmonary bypass can elevate the coronary blood ATP levels (Yellon *et al*., 1993), as well as decrease the troponin release (Alkhulaifi, 1997). Subsequent studies revealed that this type of ischemic PC can attenuate the CPB related I/R changes, such as

the increase in neutrophils, thromboxane B2, and malonedialdehyde, and increased superoxide dimultase and calcitonin gene-related peptide levels (Li *et al*., 1998b). In vitro studies using isolated or cultured myocytes revealed more evidences on the protective effects of PC on the human myocardium (Walker *et al*., 1995; Ikonomidis *et al*., 1994). PC also plays an important role in the field of heart transplantation, in which attenuation of injuries related to the hypothermic ischemia of the donor heart during harvest and preservation is very important. There have been both in vitro (Cleveland *et al*., 1996) and in vivo (Karck *et al*., 1996) studies to prove the protective effects of ischemic PC against the I/R injuries related to heart graft preservation.

Organ PC also plays an important role in abdominal viscera. In liver, since ischemia-reperfusion (I/R) is the major cause of morbidity after major resection or transplantation, PC provides a promising strategy for attenuating related injuries (Qian *et al*., 1999; Raeburn *et al*., 2001). Clamping of the portal triad (inflow occlusion) is often used during major liver resection to minimize blood loss. Several clinical and experimental studies revealed that intermittent inflow occlusion is better tolerated than prolonged continuous periods of ischemia (Horiuchi *et al*., 1995; Hardy *et al*., 1995; Isozaki *et al*., 1992). In rat model, it was found that ischemic PC can reduce both liver and lung damage following liver transplantation (Fernández *et al*., 2002). In intestine, PC was also found to have beneficial effect by delaying the development of tissue necrosis and by reduction of bacterial translocation during subsequent I/R (McCallion *et al*., 2000; Aksoyek *et al*., 2002). In kidney, ischemic PC was also proved in clinical or experimental models to have protective effects against I/R injury after renal arterial occlusion or graft preservation during transplantation (Fuller *et al*., 2005).

PC phenomena also exist in neurological tissues. In brain, researchers have found that animals exposed to brief periods of hypoxia are protected against cerebral ischemia. These phenomena can be applied, in the near future, in the field of ischemic or hypoxic injury of brain (Sharp *et al*., 2004; Chen and Simon, 1997; Kirino, 2002). Recent evidence revealed that PC with short periods of both global and focal ischemia can induce tolerance in the brain (Barone *et al*., 1998). The detailed mechanisms of PC varies in different animal species or organ systems, although in general these could be classified as the immediate acquisition which is related to post-translational modification, or delayed induction related to new protein synthesis (Kirino, 2002). These "biphasic" phenomena of PC have been observed in brain, heart, and liver tissues in human or other animals (Kirino *et al*., 1991; Bolli, 2000; Raeburn *et al*., 2001; Fernández *et al*., 2002; 2003; Harkin *et al*., 2002; Xia *et al*., 2003; Thomas *et al*., 2003). PC has also been considered as one of the protective strategies against spinal cord ischemia. Matsuyama *et al*.(1997) applied canine spinal cord ischemic PC model, with their thoracic aortas being cross-clamped for 20 min followed by formal ischemia with aortas being cross clamped for 60 min. It was found that animals undergoing ischemic PC, compared with the control group (sham operation followed by formal ischemia), can significantly attenuate the incidence of paraplegia due to spinal cord ischemia.

Ischemic or pharmacological PCs have also been proved to protect the limbs as well as the remote organs (heart, lungs) against injuries from I/R, which will occur in various clinical diseases or situations, such as peripheral arterial thromboembolism, free-flap muscle transplantation or orthopedic surgery with the use of tourniquet to block the blood flow (Papanastasiou *et al*., 1999; Harkin *et al*., 2002; Olguner *et al*., 2006).

HISTOLOGICAL AND MOLECULAR MECHANISMS OF ORGAN PRECONDITIONING

The histological and molecular mechanisms of PC have been partially uncovered. Ischemic PC protecting the tissue against subsequent ischemia-reperfusion has been demonstrated in large and small animal models (Raeburn *et al*., 2001; Peralta *et al*., 1999; Gasparri *et al*., 1999). However, this model is repugnant to doctors for clinical use. Through the realization of its molecular mechanism, ischemic PC can be replicated by pharmacologic agents through the activation of cell membrane receptors (adenosine, α-adrenergic, bradykinin, and opioid receptors) (Liu *et al*., 1991; Schulz *et al*., 1998; 2001a), administration of endogenous triggers (free radicals, nitric oxide,

calcium) (Ferrari, 1996; Post *et al*., 2000; Cain *et al*., 1999), activation of intracellular signaling pathway (PKC, TK, and MAP kinase pathway), and affecting related end effectors (metabolism, protein synthesis (e.g. heat-shock protein, Hsp), K-ATP channels, Na-K pump, and cytoskeleton) (Murry *et al*., 1990; Chen *et al*., 1997; Garlid *et al*., 1997; Freshney *et al*., 1994).

How does the PC protect the tissue from injury? The PC mechanisms described above exists in common among different organs of human as well as many other animal species. However, there still exist certain differences between different species or organ systems (Schulz *et al*., 2001a). The mechanisms of tissue ischemia-reperfusion injury are related to the cellular activation (neutrophils, T lymphocyte and antigen presenting cells (APCs)), formation of proinflammatory mediators (cytokines and chemokines), expression of adhesion molecules, activation of nitric oxide synthase (NOS) system, and the production of reactive oxygen species (ROS) (Jaeschke *et al*., 1991; Witthaut *et al*., 1994; Zhang *et al*., 1995; Sawaya *et al*., 1999; Bajt *et al*., 2001; Gujral *et al*., 2001; Jaeschke, 2003). The PC can activate various cell membrane receptors (adenosine, etc.), causing subsequent activation of intracellular signaling (PKC, TC and MAPK pathways). The final effects of PC not only triggers the increased tolerance of the cells in the myocardium, but also causes quiescent cells to participate in the cell cycles in the hepatocytes. In addition, PC can induce the production of heat shock proteins (HSPs), especially HSP70 or HSP32 (HO-1) which can reduce the nuclear binding of proinflammatory transcription factors and increase the oxidant capacity of the cells (Chen *et al*., 1997; McCormick *et al*., 2003).

Previous studies revealed myocardial ischemic PC had a biphasic phenomenon, with an early phase of protection that develops within minutes from the initial assault and lasts 2 to 3 h, and a delayed phase that becomes apparent 12 to 24 h later and lasts 3 to 4 d (Kuzuya *et al*., 1993; Marber *et al*., 1993). Unlike the early PC of myocardium, which can protect against infarction only, the delayed PC can also protect against myocardial stunning (Tyagi and Tayal, 2002; Bolli, 2000). The cascade of delayed PC in the myocardium can be subdivided into the following three major components (Bolli, 2000): (1) Triggers: the molecules that are generated during the first ischemic challenge and responsible for the initial adaptation. (2) Mediators: the molecules that are expressed in the 24 to 72 h later and responsible for conferring protection during the index ischemic challenge. (3) The intercellular signaling pathways that are activated by the triggers.

Triggers of PC (Schulz *et al*., 2001b) can be classified as follows: (1) receptor-dependent endogenous triggers, such as adenosine, bradykinin, opioids, prostaglandin (PG) and catecholamines; (2) receptor-independent endogenous triggers, such as oxygen free radicals, nitric oxide (NO), and calcium ion; (3) exogenous triggers, such as adenosine, bradykinin, opioids, oxygen free radicals, NO, PG and catecholamines. These above triggers act in episodes of preconditioning. Block in this phase will abolish the PC effect. Adenosine has been proved to play important roles in organ PC and can produce the protective effects of PC and preserve the ATP through receptor (A1) dependent or exogenous pathway (Maczewski and Beresewicz, 1998; Giannella *et al*., 1997). Pretreatment with bradykinin provides cardiac protection against free radical injury through the activation of B2 receptors (Jin and Chen, 1998). However, some other experiment also emphasized the role of endogenously produced B1 receptor in PC (Bouchard *et al*., 1998). The generation of reactive oxygen species (ROS) during the ischemic PC has also been reported to trigger delayed protection from the subsequent injury (Sun *et al*., 1996; Kaeffer *et al*., 1997; Tang *et al*., 1997; Yamashita *et al*., 1998). These animal studies showed that the administration of agents with defense mechanisms to the ROS, such as the anti-oxidants (N-2-mercaptopropionyl glycine, MPG), radical scavenger (dimethylthiourea), superoxide dimultase (SOD), or catalase plus MPG, during the initial ischemic challenge prevented the development of PC. NO generation during the initial and late ischemic PC has been proven (Bolli *et al*., 1997; Qiu *et al*., 1997). Exogenous exposure to NO can induce delayed protective effect against the myocardial infarction or stunning (Banerjee *et al*., 1999; Guo *et al*., 1999a; Hill *et al*., 2000).

The possible end effectors of PC include mediators to alter the cell energy (ATP) or substrates (carbohydrates or protein) metabolism, ion channels (K-ATP or Na-H pump) and cytoskeletons. Previous

literature has shown that PC could reduce the energy requirement during index injury, slow the accumulation of metabolites, and also reduce glycolysis. Blockade of cellular transcription (actinomycin-D) or translation (cycloheximide) was found to abolish the PC effects. Mediators (effectors) of the PC, which develop delayed protection from subsequent tissue injuries, included NO synthase (NOS), cyclooxygenase-2 (COX-2), aldose reductase, Mn-SOD, heat shock proteins (HSPs), and ATP sensitive K^+ (K-ATP) channels. K-ATP channels, which were mainly located on the sacrolemma and mitochondria, has been reported as effectors of organ protection by PC (Gross and Fryer, 1999; Grover and Garlid, 2000). Guo *et al*.(1999b) demonstrated that the late phase of ischemic PC is associated with upregulation of myocardial iNOS while eNOS remains unchanged. Thus, NO seemed to act in ischemic PC initially as the trigger (see the above paragraph) and subsequently as the mediator (Takano *et al*., 1998; Wang *et al*., 2000). COX-2 protein expression has been proved to be upregulated after ischemic PC in myocardium, concomitant with an increase in the tissue PGs levels (Shinmura *et al*., 2000). Administration of selective COX-2 inhibitor, such as celecoxib 24 h after ischemic PC, would abolish the increase in PGs and the protective effect of late PC (Guo *et al*., 2000). Previous studies revealed that NO can directly activated COX-2, which is downstream of iNOS in the preconditioned myocardium (Bolli, 2000). MnSOD induction, which might be caused by the production of ROS, TNF-α, and interleukin-1β, has been observed after heat stress or exercise (Yamashita *et al*., 1997; 1998). The mechanism of mitochondrial K-ATP protection may involve alterations in mitochondrial handling, optimization of energy production, and modulation of ROS production. The role of HSP in the PC induced tissue protection remains controversial. Some studies supported the protective role of HSP70 (Plumier *et al*., 1995; Radford *et al*., 1996), but some other studies revealed contradictory results (Yamashita *et al*., 1997; Qian *et al*., 1999). Mitochondrial K-ATP channels are not only a common downstream effector leading to PC protection but also provide positive feedback by altering upstream signals or triggers (Tyagi and Tayal, 2002).

The intracellular signaling transduction pathway of PC includes the activation of G protein and phospholipase C (in early PC) or D in delayed PC. The subsequent activation of the protein kinases (PKs) cascade pathway, in the order of protein kinase C (PKC), tyroine kinase (TK), and mitogen activated protein kinases (MAPK). These above mediators act in prolonged index ischemia or other injuries. Block in this phase will also abolish the PC effect. Activation of PKC is a crucial step because inhibition of it during PC will abolish protection at later stage (24 h later) (Baxter *et al*., 1995). The PKC activation after ischemic PC is isoform selective and ξ appears to be the specific isotype for the development (Qiu *et al*., 1998). It was found that ischemic PC selectively activates 2 members (Src and Lck) of the TKs family and that this activation is blocked by chelerythrine, suggesting that the TKs are distal to the PKC in the PC signaling transduction pathway (Ping *et al*., 1999a). MAPK superfamily is another downstream target of PKC dependent signaling during PC development, with this activation being also abolished by chelerythrine, indicating that it is downstream of PKC activation (Ping *et al*., 1999a; 1999b).

PRECONDITIONING OF THE LUNG, CURRENT EXPERIMENTAL STATUS AND CLINICAL APPLICATIONS

Previous studies on PC tolerance were mainly focused on the field of ischemia mode in cardiac or neural tissues. Since lung injuries, including ischemia-reperfusion and others, play important roles in many clinical results, including thromboembolism, trauma, thermal injury, hypovolemic and endotoxin shock, reimplantation response after organ transplantation, and many respiratory diseases in critical care. It is of interest to uncover methods, including the PCs, to protect the lung from the above injuries. However, related studies on pulmonary PC are relatively rare, so we will review previous literature about experimental and clinical studies on the pulmonary PC in the following paragraphs.

Lung ischemia-reperfusion (I/R) injury plays an important role in many clinical problems, including thromboembolism, trauma, thermal injury, hypovolemic and endotoxin shock, organ transplantation, and many respiratory diseases requiring critical care. The problem of donor organ shortage has been espe-

cially severe in clinical lung transplantation because of the scarcity of suitable donors and difficulty in lung graft preservation (Egan *et al*., 1991; Lee *et al*., 1998). Organ ischemia or hypoperfusion causes ATP exhaustion in mitochondria, with subsequent cell membrane permeability change, intracellular osmolality change, cytoskeletal and mitochondrial damage, or even cell apoptosis or necrosis. Organ reperfusion causes further worsening of injury, which is related to the interaction between neutrophil and dysfunctional endothelial cells. Subsequent changes, such as the organ free radical production, activation or the coagulation system, or further inflammatory cells adhesion and other types of tissue injuries that occur in the reperfusion stage (Becker *et al*., 1992; 1998; Seeger *et al*., 1994; Luh *et al*., 1999; 2000; 2002; 2004). Preconditioning can reduce the ischemia-reperfusion injury in solid organs such as the heart, liver, kidney and bones. However, there are relatively limited data on similar effects on lungs (Gasparri *et al*., 1999; Soncul *et al*., 1999; Du *et al*., 1996; Featherstone *et al*., 2000; Schutte *et al*., 2001; Neely and Keith, 1995; Huang *et al*., 2002; Waldow *et al*., 2004).

The protection provided by ischemic PC against I/R injuries of the lung had been reported in previous literature. In experimental guinea pig (Soncul *et al*., 1999), canine (Li *et al*., 1998b; Friedrich *et al*., 2001), and rabbit (Li *et al*., 1999; Gasparri *et al*., 1999; Zhang *et al*., 2003) models, it was found that ischemic PC by blocking the pulmonary hilar blood flow can attenuate the pulmonary dysfunction related to exposure to subsequent I/R. Blockade of the pulmonary ventilation alone as the model of PC, in the rat model, can achieve similar effects as traditional ischemic PC which block both pulmonary blood flow and ventilation (Featherstone *et al*., 2000). There was consensus on the timings of ischemic PC, which were usually immediately before the index I/R. However, the duration or number of cycles of ischemic PC varied. In rabbit in vivo lung ischemia model lung ischemia was performed by blocking the hilum of the left lung for 10 min and then release for 15 min (Li *et al*., 1999). In similar rabbit model, 15 min of ischemic PC is better than 5 min of it. However, repeated cycles appear slightly better single episode of ischemic PC (Gasparri *et al*., 1999). In canine model, the duration of ischemic PC was 10 min (Li *et al*., 1998b), which was similar to the rabbit model. However, another study showed that in rabbit model ischemic PC 5 min was better than 10 min for the protection of subsequent I/R (Friedrich *et al*., 2001). Ischmic PC, in which the pulmonary hilum is usually clamped for 10 min with subsequent 10 min of reperfusion, has also been applied in clinical conditions, such as people undergoing major lung resection (Yang *et al*., 2002; Chen *et al*., 1999) or isolated lung perfusion with chemotherapeutic agents for unresectable cancer or metastatic sarcoma (Zhang and Chen, 2001).

The possible protective mechanisms of ischemic PC included inhibition of inflammatory cytokines such as TNFα, IL-6 and IL-8, with subsequent reducing activation and infiltration of neutrophils (Zhang *et al*., 2003), decrease of lipid peroxidation (Soncul *et al*., 1999), reduction of apoptosis of lung cells in vivo by upregulating bcl-2 protein expression (Yang *et al*., 2002), increasing production of endogenous calcitonin gene related peptide (CGRP) (Chen *et al*., 1999), reducing production of oxygen free radicals (Li *et al*., 1998b). In summary, ischemic PC can attenuate the I/R related changes, such as the increase in neutrophils, thromboxane B2, and malonedialdehyde, and increased superoxide dimultase and calcitonin gene-related peptide levels. Preconditioning also preserves better pulmonary functions with higher arterial oxygen tension, lower pulmonary arterial pressure and pulmonary vascular resistance, and less lung injury on histological findings (Li *et al*., 2001).

Systemic ischemia or ischemia from remote organs could also result in pulmonary injuries after reperfusion. There are some experimental studies to reveal ischemic PC of the heart in rabbit model (Zhang *et al*., 1998), liver in rat model (Fernández *et al*., 2002; 2003), limb in sheep or pig model (Xia *et al*., 2003; Harkin *et al*., 2002) can attenuate pulmonary dysfunction after various types of reperfusion injuries, such as cardiopulmonary bypass (CPB), off-pump coronary arterial bypass (OPCAB) surgery, liver transplantation, hemorrhagic shock (Pittet *et al*., 2002), or limb I/R.

Several types of PC other than ischemia for lung have been reported in previous literature. Hyperthermia has been applied as a common type of PC. Traditional model of hyperthermic PC in rat is 41 °C for 15 min (Huang *et al*., 2002; Thomas *et al*., 2003).

However, this model would result in more cellular damage. A less severe thermal PC, using water bath to elevate core temperature by 1 °C for 15 min for 5 consecutive days, can also achieve PC protective effects (McCormick *et al*., 2003). Hyperthermal PC can attenuate pulmonary dysfunction after various animal models of injuries mimicking clinical conditions, such as organ transplantation, pulmonary air emboli, hemorrhagic shock, or abdominal surgery. Whole body hypoxic PC can protect mice against acute lethal hypoxia. This protection involves preservation of vital organ functions (Zhang *et al*., 2004) and phosphotidylinositol 3 kinase (PI-3K) plays important roles in the development of resistance against subsequent injury (Ahmad *et al*., 2003).

Pharmacological agents, following the discovery of related molecular mechanisms of PC, gradually replace ischemia or hyperthermia, as the specific "targeted" pretreatment methods to protect organs from various types of injuries. In rat model, PC with diethylmaleate (DEM), an intracellular pro-oxidant agent, can protect against I/R-induced lung injury (Kiely *et al*., 2002). Stress PC with geldanamycin in rat model could restore a normal function of the alveolar epithelium in the early phase following hemorrhagic shock by attenuating NO mediated oxidative stress to the lung epithelium (Pittet *et al*., 2002). In isolated lung perfusion of rat model, PC with intravenous administration of 3-nitropropionate (an inhibitor of the mitochondrial complex II) (Hirata *et al*., 2001), or N-acetyl-L-cysteine (NAC, an oxidant scavenger which promotes glutathione (GSH)) (Weinbroum *et al*., 2001), can prevent lung from cold or warm I/R injury. Lung reperfusion injury from ischemia of remote organ, such as intestine, can also be ameliorated by PC with pharmacological agents, such as doxorubicin, an inducer of heme oxygenase-1 (HO-1, a stress protein) (Ito *et al*., 2003). Moreover, these protective effects could be abolished by the administration of HO-1 inhibitor, such as tin protoporphyrin (Sn-PP) (Tamion *et al*., 2002).

Nitric oxide (NO), a potent vasodilator which can be synthesized in various tissues (such as endothelia, neural tissues, or inflammatory cells), could also be administered as a method of pulmonary PC. In porcine lung in situ normothermic I/R model, it was found that PC with NO inhalation 10~15 min prior to ischemia can protect against pulmonary hypertension, impaired gas exchange, and the inflammatory response of pulmonary I/R injury (Waldow *et al*., 2004). Short term (30 min) and low dose (10×10^{-6}) pre-ischemia NO inhalation for I/R injury in buffer-perfused rabbit lungs, subsequently undergoing 210 min of warm, anoxic ventilated ischemia. This NO PC maintains endothelial integrity in a subsequent I/R largely responsible to the nonvasodilatory and non-cGMP-related mechanisms (Schutte *et al*., 2001).

CONTROVERSIES IN THE RESEARCHES AND CLINICAL APPLICATIONS OF PC

The mechanisms of PC have been best studied in the heart and brain. These cellular mechanisms and protective strategies are still developing in other organs, including the lung. There are still many controversies on the effects of preconditioning for the following reasons (Schulz *et al*., 2001b) making more related researches necessary. (1) PC phenomena has differences among species. For example, the functional role for PKC isoenzymes differs among species, with PKCε being most important in rabbits, PKCδ in rats and PKCα in dogs. It appears that results from large mammals are closer to those from humans. (2) Different experimental models (in vitro versus in vivo, anesthetized versus conscious animals) will affect the results. (3) The age of the animals or human beings will also affect the results. (4) Modes of PC, such as the cycles and duration of the preconditioning stimuli, low flow vs no flow and regional vs global ischemia will also affect the results. The site of blockade (redundant or non-redundant signaling pathway) will also yield different results. (5) The results of pharmacologic agents are valuable tools for discovering the mechanisms of PC. However, the results will be influenced by the effectiveness and specificity of the drugs for a given target at a given concentration. (6) The intraspecies differences, the rate of transfection, the redundancy of the signaling pathway should be considered in experiments on transgenic or transfective approaches.

CONCLUSION

PCs with protective roles in many organ systems

against various types of injuries have been found. Their histological and molecular mechanisms have been gradually uncovered through a series of studies over the past decade. Though related studies in the lung are still much less than studies on the other organs, such as heart or brain, it is still of clinical importance to develop related researches on the lung. More experimental and clinical studies on PCs are needed to be carried out in the future to determine their benefits in attenuating subsequent organ injury.

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