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Inhibition of Pre-B Cell Colony Enhancing Factor Protects Against Lung Injury Following Cardiopulmonary Bypass in Rats

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ABSTRACT

Pre-B cell colony enhancing factor (PBEF) is recognized as a proinflammatory cytokine involved in acute lung injury, but its contribution to lung damage following cardiopulmonary bypass (CPB) has not been clarified. This study explored how reducing PBEF expression affects lung injury and the regulation of sodium and water transport in a rat model of CPB. Lung morphology was examined using hematoxylin and eosin staining. Immunohistochemistry was applied to assess PBEF levels. Western blotting was used to measure proteins related to sodium–water balance and to analyze associated signaling pathways. Rats subjected to CPB displayed marked alveolar wall injury and increased free PBEF levels compared with controls. CPB also led to elevated expression of PBEF, surfactant protein D, aquaporin 1, aquaporin 5, and the epithelial sodium channel. Administering an adenovirus carrying sh-PBEF lowered the expression of these proteins in CPB-treated rats. In addition, phosphorylation of ERK1/2, AKT, and p38 MAPK was heightened after CPB but decreased following sh-PBEF treatment. Delivering sh-PBEF through an adenoviral vector may help lessen CPB-induced lung damage and improve sodium and water transport in the lungs, possibly by suppressing MAPK, ERK1/2, and AKT signaling pathways.

Keywords: Epithelial sodium channel, Pre-B cell colony enhancing factor, Aquaporin, Cardiopulmonary bypass Introduction

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Introduction

Cardiopulmonary bypass (CPB) is routinely used during major surgeries to help control blood loss [1] and may contribute to lowering neurological complications [2]. Even so, CPB is still associated with a considerable risk of brain injury and postoperative abnormalities in many patients [3, 4]. Among the complications that follow CPB, pulmonary edema plays a central role in the onset of acute lung injury (ALI) [5]. This occurs largely because CPB increases the permeability of the alveolar–capillary barrier while reducing the ability of the lungs to clear fluid. When alveolar fluid removal is delayed, postoperative pulmonary function and lung perfusion can deteriorate [6, 7].

Fluid transport across the alveolar epithelium depends mainly on epithelial sodium channels (ENaC) and aquaporins (AQPs). ENaC allows sodium ions to enter the alveolar epithelial cells and then move out through the basolateral membrane into the lung interstitium [8]. This outward movement of sodium creates a strong electrochemical gradient, which in turn drives water and chloride (Cl^-) to follow passively [9, 10]. Water transport is further supported by AQPs located on the epithelial cell surface [11].

Several signaling mechanisms have been identified that regulate ENaC and AQP expression [8]. For example, ENaC and TGF-β1 can reduce α-ENaC levels in human and rat alveolar epithelial cells through ERK1/2 activity, thereby decreasing amiloride-sensitive sodium transport [12]. In LPS-induced ALI, 17β-estradiol has been shown to limit pulmonary edema and enhance ENaC expression through activation of the PI3K/AKT/SGK1 pathway

[13]. Inflammatory cytokines such as IL-6, IL-8, and TNF-α can also decrease AQP1 levels via MAPK signaling, leading to impaired fluid regulation [14].

Pre-B cell colony enhancing factor (PBEF) is a nicotinamide phosphoribosyl transferase [15] involved in NAD^+ biosynthesis and also participates in immune and inflammatory regulation [16–18]. Elevated PBEF expression has been documented during ALI, accompanied by increased levels of TNF-α, IL-1β, TGF-β1, and other inflammatory mediators in the lung. These changes can disrupt the sodium–water transport machinery in alveolar epithelial cells, resulting in reduced ENaC and AQP expression [19–21].

The present study investigated lung tissue alterations in rats subjected to CPB and examined how PBEF influences sodium and water transport in the lungs. Possible signaling pathways involved in this regulation were also explored. The findings may provide insight into potential strategies to reduce CPB-related lung injury.

Follow-up procedures

All subsequent measurements were performed 4 hours after the injection.

Determination of lung dry-to-wet weight ratio

Fresh lung tissue was first weighed and then dried in an incubator at 60°C for 24 hours. After drying, the tissue was weighed again. The dry-to-wet (D/W) weight ratio was calculated using the initial wet weight. Each sample was measured three times, and the average value was used for analysis [22].

Assessment of Na^+–K^+–ATPase activity

The activity of Na^+–K^+–ATPase was determined using a commercial assay kit (Solarbio, Beijing, China), following the manufacturer's protocol.

Hematoxylin and eosin (HE) staining

Lung samples were fixed overnight in 4% paraformaldehyde at 4°C. The tissues were then dehydrated through a graded ethanol series (70%, 80%, and 90%), followed by immersion in a mixture of ethanol and xylene for 15 minutes, xylene I for 15 minutes, and xylene II for another 15 minutes. After clearing, the tissues were placed in xylene–paraffin and then into two paraffin baths (50 and 60 minutes). Paraffin blocks were sectioned at 20 μm, dried, and subsequently dewaxed and rehydrated. Sections were stained with hematoxylin for 3 minutes and eosin for 3 minutes. After mounting, the slides were examined using a light microscope, and at least four representative fields were captured for each specimen. Lung injury scoring was performed using previously published criteria [23].

Immunohistochemistry

Sections prepared as described above were incubated overnight at 4°C with a monoclonal antibody against PBEF (1:200, 11776-1-AP, Proteintech). Secondary labeling was performed with HRP-conjugated goat anti-rabbit IgG (1:10,000; A16104SAMPLE, Thermo Fisher Scientific) and Alexa Fluor 593–conjugated goat anti-mouse IgG (Life Technologies) for 30 minutes at room temperature. Images were obtained using a BX51 light microscope (Olympus, Japan). Protein expression quantification followed established methods in the literature [24].

Western blotting

Proteins were isolated from liver tissues, and concentrations were measured using the bicinchoninic acid assay. Equal amounts of protein (20 μg per sample) were separated on 12% SDS–polyacrylamide gels and transferred to PVDF membranes. After blocking with 5% skim milk, membranes were incubated overnight at 4°C with primary antibodies targeting PBEF, ERK1/2, phospho-ERK1/2, p38 MAPK, phospho-p38 MAPK, AKT, phospho-AKT, AQP1, AQP5, ENaC, surfactant protein D (SP), and GAPDH (details and dilutions as originally provided). Appropriate secondary antibodies were applied before visualization.

Statistical analysis

Data are presented as mean ± standard deviation and were analyzed using SPSS 19.0. Because CPB-induced lung injury and LPS-induced lung injury may involve different biological mechanisms, analyses for CPB-related groups and LPS-related groups were performed separately. One-way ANOVA followed by the Newman–Keuls post hoc test was used. A p-value <0.05 was considered statistically significant.

Results and Discussion

Heart rate and mean arterial pressure

Following initiation of CPB, the rats maintained stable physiological parameters. After 30 minutes, controlled cooling lowered the body temperature to 20–23°C to induce deep hypothermic circulatory arrest. During this period, cardiac activity gradually slowed. Once rewarming was completed, blood pressure and heart rate returned to baseline values. After CPB was discontinued and the catheters removed, all rats recovered normally. When anesthesia subsided, they resumed free access to food and water. Heart rate and mean arterial pressure measurements are summarized in **Table 1.**

Table 1. Heart Rate and Mean Arterial Pressure During Cardiopulmonary Bypass in Rats (Mean±SD)

	Heart Rate (Beats/min)	Mean Arterial Pressure (mmHg)
Cardiopulmonary bypass	338.75±65.721	101.23±16.375
After cooling down	91.724±23.672	82.23±9.461
After rewarming	319.764±51.658	94.75±13.382

Compared with controls, the ratio of dry:wet weight increased in the CPB group and LPS group. Sh-PBEF reduced the increase of dry:wet ratio caused by CPB, but not LPS **(Figure 1)**.

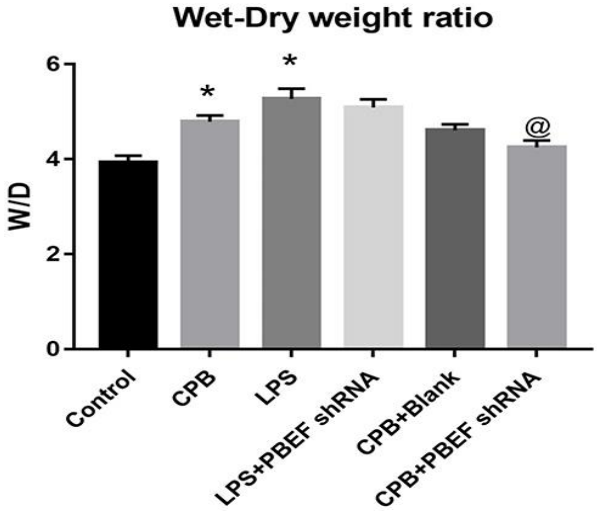
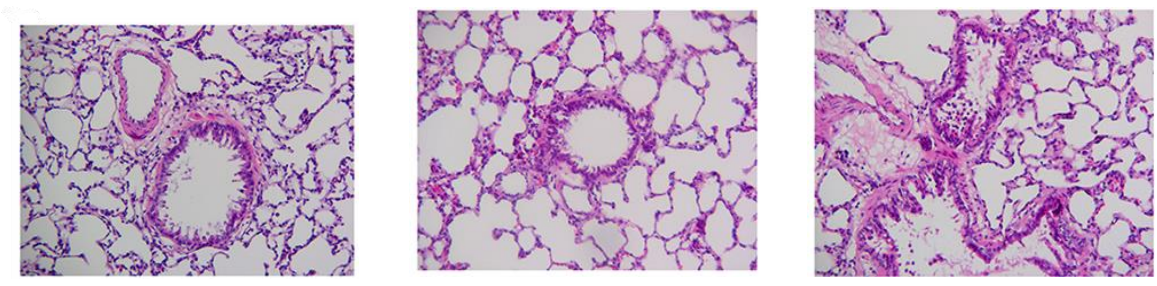


Figure 1. Adenovirus-encoding sh-PBEF reduced the dry:wet (D/W) tissue ratio vs control, *P<0.05; vs CPB+Blank, @P<0.05.

Abbreviations: PBEF, pre-B cell colony enhancing factor; CPB, cardiopulmonary bypass.

Pathological changes of lung tissues

The lung alveoli in rats that underwent CPB and were then treated with LPS showed clear damage when compared to the control group **(Figure 2)**. In contrast, the lung tissues of the control, blank, and PBEF shRNA groups showed no noticeable pathological changes. The adenovirus carrying sh-PBEF, unlike the empty vector, significantly reduced the lung tissue injury caused by CPB or LPS treatment.



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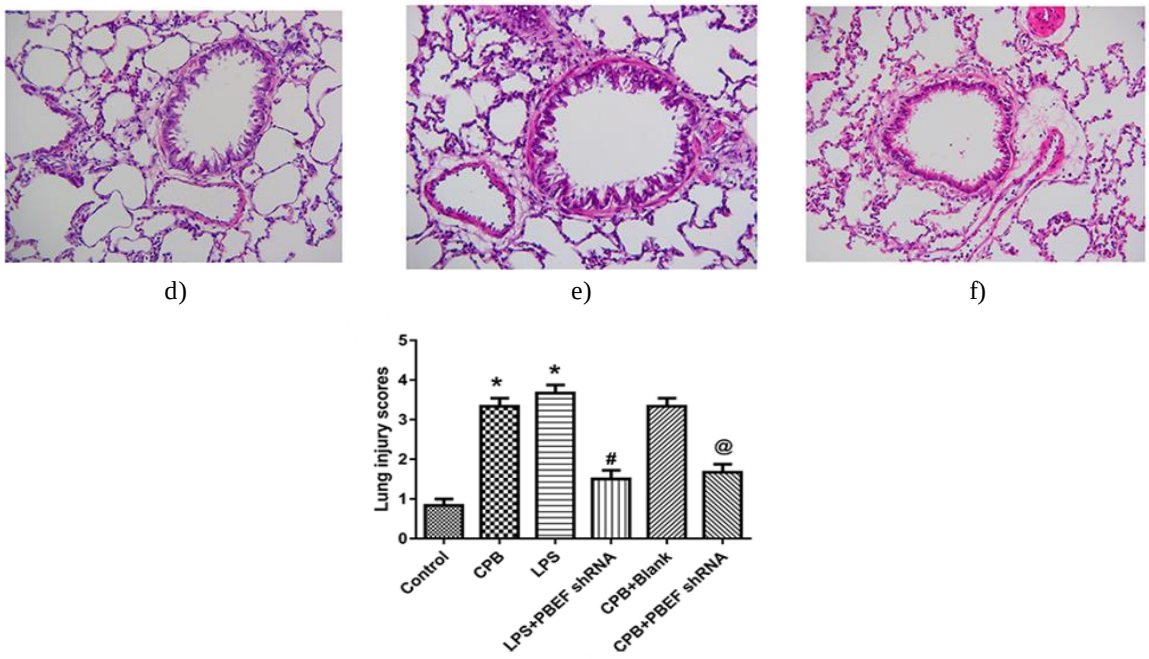
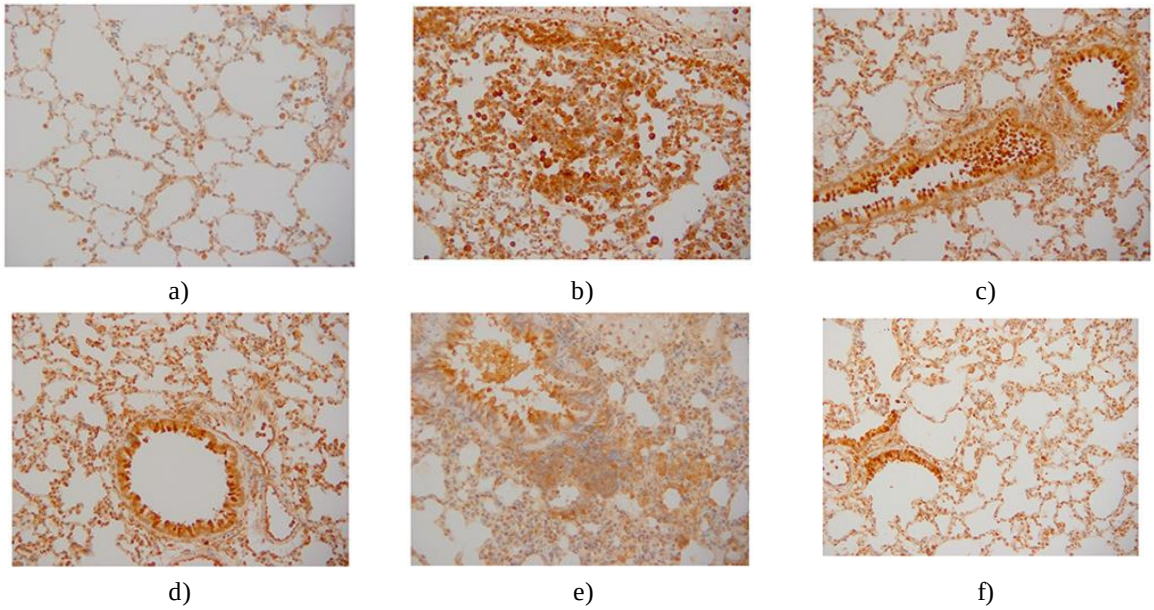


Figure 2. shows how the lung tissue changed in each group. Using HE staining, it was clear that rats exposed to CPB and given LPS had noticeable injury in their lung alveoli. In the control, blank, and PBEF shRNA groups, the lung structure looked normal with no clear signs of damage. Treatment with adenovirus carrying sh-PBEF helped protect the lungs and lessened the injury caused by CPB or LPS.
(a): Control; (b): CPB; (c): LPS; (d): LPS+PBEF shRNA; (e): CPB+Blank; (f): CPB+PBEF shRNA (Magnification: ×200); (g): Lung injury scores vs control, *P<0.05; vs LPS, #P<0.05; vs CPB+Blank, @P<0.05.
Abbreviations: PBEF, pre-B cell colony enhancing factor; CPB, cardiopulmonary bypass.

Adenovirus-encoding sh-PBEF reduced the increase of PBEF caused by CPB

Figure 3 displays the IHC staining for PBEF in lung tissues. PBEF appeared in many areas of the lung, and its levels were higher in the endobronchial wall and in scattered free cells in rats treated with CPB or LPS. When adenovirus-encoding sh-PBEF was used, it lowered the CPB-related rise in PBEF expression.



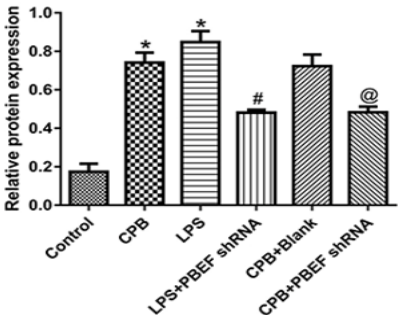


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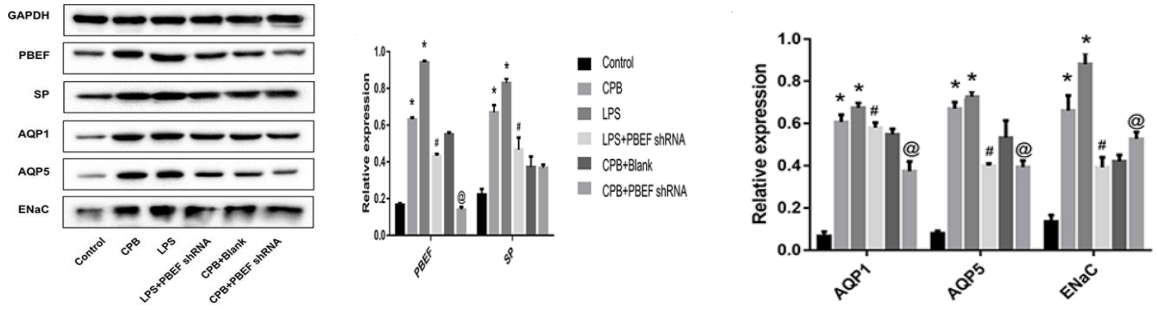
Figure 3. Effect of Adenovirus-Encoding sh-PBEF on PBEF Expression in Lungs
Immunohistochemistry revealed that PBEF was present throughout lung tissue, mostly in a free form. Rats that underwent CPB showed noticeably higher levels of PBEF than rats without CPB. Treating rats with adenovirus carrying sh-PBEF markedly lowered PBEF expression induced by CPB. In the staining, PBEF appeared brown and nuclei were blue.
(a): Control; (b): CPB; (c): LPS; (d): LPS+PBEF shRNA; (e): CPB+Blank; (f): CPB+PBEF shRNA (Magnification: ×200); (g): Relative protein expression vs control, *P<0.05; vs LPS, #P<0.05; vs CPB+Blank, @P<0.05.
Abbreviations: PBEF, pre-B cell colony enhancing factor; CPB, cardiopulmonary bypass

Effect of sh-PBEF on lung proteins: α-PBEF, SP, AQP1, AQP5, and ENaC
Protein analysis showed that CPB or LPS caused a significant increase in PBEF, SP, AQP1, AQP5, and ENaC levels in lung tissue compared to controls. When sh-PBEF was administered, the elevated levels of PBEF, SP, AQP1, and AQP5 were reduced. Additionally, sh-PBEF lowered the increase in ENaC caused by LPS, demonstrating its protective effect on lung fluid regulation.



a) b) c)

Figure 4. Adenovirus-encoding sh-PBEF reduced the increase of α-subunit of PBEF, SP, AQP1, AQP5, and ENaC in lung tissue. (a) Representative blots; (b) Relative expression of PBEF and SP; (c) Relative expression of AQP1, AQP5, and ENaC; vs control, *P<0.05; vs LPS, #P<0.05; vs CPB+Blank, @P<0.05.
Abbreviations: PBEF, pre-B cell colony enhancing factor; CPB, cardiopulmonary bypass.

Effects of adenovirus-encoding sh-PBEF on Na^+-K^+-ATPase activity of lung tissue
Na^+-K^+-ATPase activity in lung tissue was up-regulated in CPB and LPS groups, while sh-PBEF down-regulated the activity caused by LPS, but not by CPB **(Figure 5)**.

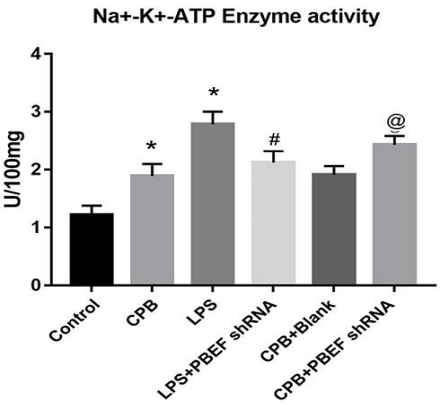


Figure 5. Impact of Adenovirus-Encoding sh-PBEF on Lung Na^+–K^+–ATPase Activity
Na^+–K^+–ATPase activity in lung tissue was measured across the experimental groups. CPB or LPS treatment caused a noticeable decrease in enzyme activity compared with the control group. Treatment with adenovirus carrying sh-PBEF partially restored Na^+–K^+–ATPase function, counteracting the effects of CPB or LPS.
P<0.05 vs control; #P<0.05 vs LPS; @P<0.05 vs CPB+Blank.
Abbreviations: PBEF, pre-B cell colony enhancing factor; CPB, cardiopulmonary bypass.

Adenovirus-encoding sh-PBEF attenuates phosphorylation of ERK1/2, Akt, and p38 MAPK
Rats exposed to CPB or LPS showed a significant rise in phosphorylation levels of ERK1/2, Akt, and p38 MAPK in lung tissue compared with controls. Administration of adenovirus-encoding sh-PBEF markedly reduced these phosphorylation levels, indicating that sh-PBEF can suppress the activation of these signaling pathways **(Figure 6)**.

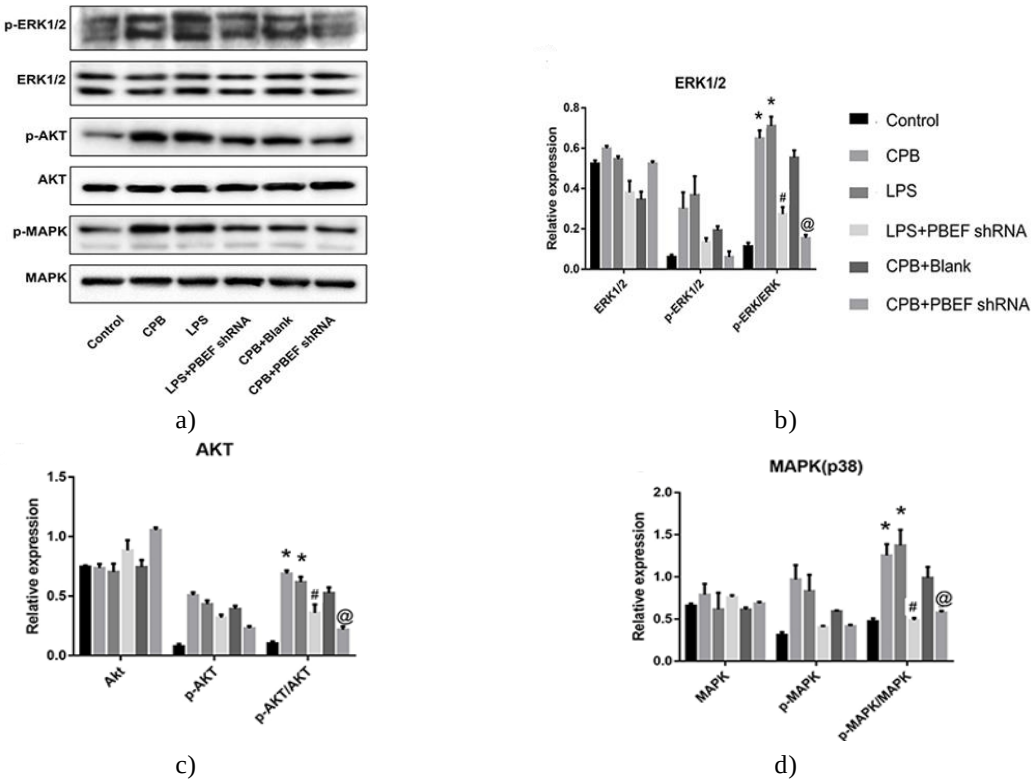


Figure 6. Adenovirus-Encoding sh-PBEF Attenuates Phosphorylation of ERK1/2, Akt, and p38 MAPK in Rat Lung Tissue
(a) Representative Western blots; (b) ERK1/2 phosphorylation; (c) Akt phosphorylation; (d) p38 MAPK phosphorylation versus control.
P<0.05 vs control; #P<0.05 vs LPS; @P<0.05 vs CPB+Blank.
Abbreviations: PBEF, pre-B cell colony enhancing factor; CPB, cardiopulmonary bypass.

Previous in vitro studies using human umbilical vein endothelial cells under hypoxic conditions demonstrated that PBEF expression rises in response to hypoxia. Elevated PBEF was associated with increased cell permeability, which could be mitigated by adenovirus-mediated sh-PBEF via inhibition of the MAPK and ERK signaling pathways [25, 26]. Additionally, PBEF has been shown to suppress sodium–water transport-related proteins in type I and II alveolar epithelial cells in rats [8, 27].

However, much of the prior evidence comes from cell culture models. To examine the role of PBEF in pulmonary edema clearance in vivo, an animal CPB model was established. Using a rat DHCA model, as described by Waterbury *et al*. [28], we effectively simulated clinical circulatory arrest conditions. Physical cooling of the rats reduced heart pumping and pulmonary perfusion, creating conditions comparable to clinical CPB-induced lung injury. For comparison, an inflammatory lung injury model was induced via tail vein injection of LPS, a well-established method for eliciting pulmonary inflammation [29, 30]. HE staining revealed that LPS induced marked alveolar wall deformation and interstitial swelling, whereas CPB produced milder histological changes. Biochemical analysis confirmed that PBEF was upregulated in both models, suggesting that CPB in this study induced moderate pulmonary edema.

As a proinflammatory cytokine, PBEF is predominantly expressed in neutrophils and lymphoid cells [31]. Immunohistochemistry revealed that PBEF was present in alveolar walls, bronchial walls, and alveolar spaces, likely representing infiltrating immune cells, indicating local lung inflammation.

Reducing PBEF expression inhibited phosphorylation of ERK1/2, Akt, and p38 MAPK and decreased levels of the α-subunit of PBEF, AQP1, AQP5, and ENaC. These results are consistent with previous reports [8, 19]. While PBEF suppresses AQPs and ENaC, it also positively regulates ERK1/2, Akt, and p38 MAPK phosphorylation, aligning with earlier studies [8, 19]. Pulmonary edema models typically produce strong inflammatory responses in epithelial cells; here, the CPB model simulated mild lung injury, resembling postoperative conditions rather than severe inflammation.

The PI3K/Akt pathway is crucial for cell survival, neuronal plasticity, and other cellular functions [32–34]. Its activation supports expression of ENaC and AQPs, reducing fluid accumulation in vivo [13, 35]. PBEF activates both PI3K/Akt and MAPK/ERK pathways [8]. In this study, under DHCA-assisted CPB, PBEF appeared to promote lung fluid transport mainly through these pathways, supporting our prior findings using specific inhibitors [8].

We also assessed SP expression in lung tissue. SP, expressed in alveoli, reduces surface tension, protects against inhaled pathogens, and limits inflammation-mediated alveolar damage [36]. Under CPB, SP levels increased, reflecting its protective role. PBEF inhibition had minimal effect on SP during CPB but reduced SP under LPS stimulation, suggesting additional upstream regulatory mechanisms independent of ERK, Akt, and MAPK pathways.

Interestingly, inhibiting PBEF consistently reduced phosphorylation of ERK, Akt, and p38 MAPK and decreased AQP1, AQP5, ENaC, NKA, and SP expression. In CPB, while AQP1 and AQP5 were downregulated, ENaC and NKA activity slightly increased, and SP remained unchanged. In contrast, sh-PBEF effectively reduced LPS-induced protein changes, but not those from CPB, highlighting areas for future investigation.

Conclusion

In summary, PBEF serves as a potential biomarker for lung injury following CPB. Reducing its expression restores sodium–water transport function and mitigates pulmonary edema, likely through modulation of MAPK, ERK1/2, and Akt signaling pathways.

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Conflict of Interest: None

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Ethics Statement: None

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