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Therapeutic efficacy of dexmedetomidine on chronic obstructive pulmonary disease *via* downregulating lncRNA PACER

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Abstract. – OBJECTIVE: The aim of the study was to clarify the therapeutic mechanism of Dexmedetomidine (DEX) on the chronic obstructive pulmonary disease (COPD) and its regulatory effect on long non-coding RNA (lncRNA) PACER.

PATIENTS AND METHODS: Serum level of PACER in COPD patients was detected by quantitative real-time polymerase chain reaction (qRT-PCR). The diagnostic potential of PACER in COPD was assessed by plotting ROC curves. The *in vivo* COPD model was generated in rats by cigarette smoking exposure. Primary rat alveolar epithelial cells were isolated, purified and cultured. After overexpression of PACER in primary rat alveolar epithelial cells, proliferative and migratory abilities were assessed by cell counting kit-8 (CCK-8) and transwell assay, respectively. Subsequently, we detected changes in PACER expression, viability and migratory potentials in primary rat alveolar epithelial cells harvested from control rats, and those harvested from COPD rats and induced with either DEX or not. Rescue experiments were conducted to uncover the involvement of PP2A in PACER-regulated cell phenotypes.

RESULTS: PACER was upregulated in serum of COPD patients, which was a potential biomarker for diagnosing COPD. Overexpression of PACER in primary rat alveolar epithelial cells enhanced proliferative and migratory abilities. Compared with primary rat alveolar epithelial cells harvested from control rats, proliferative and migratory abilities were stronger in those harvested from COPD rats and induced with either DEX or not. Notably, DEX induction decreased PACER expression, and proliferative and migratory abilities in primary rat alveolar epithelial cells harvested from COPD rats. Overexpression of PP2A could partially abolish the promotive effects of PACER on proliferative and migratory abilities in DEX-induced primary rat alveolar epithelial cells harvested from COPD rats.

CONCLUSIONS: PACER drives the proliferative and migratory abilities of alveolar epithelial cells through activating PP2A. Dexmedetomidine is conducive to COPD treatment by downregulating PACER.

Key Words:
COPD, Alveolar epithelial cells, Dexmedetomidine, PACER, PP2A.

Introduction

Chronic obstructive pulmonary disease (COPD) is featured by chronic bronchitis and/or emphysema resulted from airway and lung injuries. COPD can aggravate heart disease and respiratory failure. Abnormal inflammatory response caused by toxic gases or harmful particles targeting airway and lung tissues attributes to the pathogenesis of COPD. It has high incidence, disability and mortality, posing a great burden on the society[1,2].

Dexmedetomidine (Dex) is a new type of highly selective α2 adrenergic receptor agonist, belonging to imidazole derivatives[3]. Dex has been widely used in intensive care unit (ICU) and perioperative anesthesia. It exerts a protective effect on the brain, heart, kidney, liver, lung and other important organs through suppressing

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apoptosis, inflammation and oxidative stress[4,5]. It is confirmed that Dex can effectively protect inflammation-induced lung injury[6-8].

Long non-coding RNAs (lncRNAs) are non-coding RNAs with more than 200 nt long. Abnormally expressed lncRNAs are closely related to disease progression[9-12]. Through targeting the downstream genes, lncRNAs are capable of either inducing or inhibiting inflammatory response. Multiple lncRNAs have been identified to have a relation to COPD[13]. Very recently, lipopolysaccharide-induced lncRNA PACER (p50-associated COX-2 extragenic RNA) is found to aggravate inflammatory response by activating NF-κB and thus enhancing COX-2 expression[14,15]. This study aims to uncover the potential function of Dex in improving COPD and the involvement of PACER.

Patients and Methods

Patients

This investigation was approved by the Ethics Committee of First Affiliated Hospital of Kunming Medical University. Signed written informed consents were obtained from all participants before the study. Fifty-five COPD patients admitted in First Affiliated Hospital of Kunming Medical University from May 2017 to June 2019 were enrolled. Through asking for medical history, physical examinations, X-ray diagnosis and pulmonary function test (PFT), COPD cases were confirmed according to the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary[16]. Specifically, diagnostic criteria were as follows: (1) Exposure history of susceptible factors, including history of smoking, exposure to occupational dust, chemical substance or air pollution; (2) Long-term history (more than 2 years) of chronic cough, expectoration, and shortness of breath, with more than 3 months of attacks each year; (3) Incompletely reversible airflow restriction. PFT showed a FEV_1 less than 70% of predicted, and $FEV_1/FVC \leq 70\%$; (4) Imaging examinations (X-ray or chest CT) supported the findings of chronic bronchitis and emphysema; (5) Sudden deterioration of cough, expectoration and shortness of breath. Exclusion criteria were as follows: (1) chest diseases other than COPD, including bronchiectasis, bronchial asthma, pleural effusion, pleural adhesions, pneumothorax, interstitial lung disease, and active pulmonary nodules; (2) imaging examinations supported the findings of evident pneumonia; (3) heart diseases, including rheumatic heart disease, myocardial disease, myocardial infarction and congestive heart failure; (4) consumptive diseases, including diabetes mellitus, hyperthyroidism and malignant tumors; (5) immune diseases, including HIV, rheumatoid arthritis and systemic lupus erythematosus; (6) liver and kidney failure; (7) sequelae of stroke; (8) operation, fire burn or trauma within 6 months, and strenuous exercise within 2 weeks; (9) previous history of lobectomy; (10) intolerable with examinations because of poor physical condition. A total of 45 healthy subjects during the same period were recruited as controls.

Blood Sample Collection

After overnight fast, 3-5 ml of venous blood was collected in each subject in the morning. The blood was centrifuged at 4°C, 5,200 r/min for 10 min. The upper layer was collected and labeled for preservation at -80°C.

COPD Model in Rats

Sprague-Dawley (SD) rats were housed in a standard environment with 12 h of light/dark cycle and room temperature of 26°C. Rats were given to free access to food and water. Twenty rats were kept in a chamber (110 cm × 86 cm × 72 cm) with cigarette smoking (CS). Briefly, 20 cigarettes were lighted. Each cigarette was smoked once per minute for 30 s, and the mainstream and side-stream CS flow were introduced to the chamber through a plastic hose. The fan in the chamber was turned on for 10 s with an interval of 50 s, making the CS distribution even. After 8-min CS exposure, the smoking system was turned off. Rats in COPD group were exposed to CS for three times per day, with 1 h each time. CS exposure was conducted five days per week for consecutive 16 weeks. During CS exposure, rats in the chamber were free to have food and water. Rats in control group (n=10) were similarly treated with fresh air. This investigation was approved by the Animal Ethics Committee of Henan University Animal Center.

PFT

Rats were anesthetized by 10% chloral hydrate (10 mL/100 g) through intraperitoneal administration. They were fixed on the surgical table in the supine position. The neck skin was longitudinally cut to expose neck and infrahyoid muscles. The trachea and esophagus were carefully separated and fixed using silk thread. An inverted T-shaped incision was made at the

two trachea rings under the cricoid cartilage for trachea intubation and fixation. A transverse incision was cut in the upper of rat esophagus for esophageal intubation. A small amount of normal saline was administrated in the tube for removal of air bubbles in the esophagus. Airway and esophageal pressure sensor probes of the small animal spirometer were fixed in the trachea. TV (tidal volume), PEF (peak expiratory flow), EF_{50} (maximal expiratory flow in 50% vital capacity), $FEV_{0.3}$ (forced expiratory volume in 0.3 seconds), and $FEV_{0.3}$/FVC (forced vital capacity) were continuously monitored for 30 min. The average PFT indicators were recorded.

ABG Analysis

Rats were anesthetized by 10% chloral hydrate (10 mL/100 g) through intraperitoneal administration. Intubation of abdominal aorta was performed. 1 ml of arterial blood was collected using the pre-heparinized sterile injector and sealed by a rubber stopper for arterial blood gas (ABG) analysis.

Isolation of Primary Rat Alveolar Epithelial Cells, Purification, Drug Induction and Transfection

Isolation

Rats were anesthetized by 10% chloral hydrate (10 mL/100 g) through intraperitoneal administration. They were fixed on the surgical table in the supine position. Tracheotomy and intubation were conducted. After exposing the thoracic cavity, pulmonary artery lavage was performed using 50 mL of normal saline, aiming to clean the vascular bed. Bilateral lungs were harvested and placed in culture dishes. Alveolar lavage using 10 mL of normal saline was repeated for 5 times, followed by digestion in 15 mL of trypsin in water bath at 37°C. Ten minutes later, lungs were cut into small pieces (1 mm^3) and digested in 0.025% DNase, which was terminated by adding 5 mL of Dulbecco's Modified Eagle's Medium (DMEM; Gibco, Rockville, MD, USA). The mixture was gently shaken with 20 mL of buffer in water bath at 37°C. Five minutes later, tissue suspension was successively filtered by 150 μm, 20 μm and 10 μm sieves, respectively. Finally, the suspension was centrifuged at a low temperature for 8 min. The precipitant was suspended in DMEM.

Purification

In a 25 cm^2 culture bottle, 1.5 mg anti-mouse IgG dissolved in 50 mmol/L Tris buffer was added. The culture bottle was placed in water bath at 37°C for 2 h, followed by rinsing with phosphate-buffered saline (PBS) twice and serum-free DMEM once. Lung tissue suspension was applied in the IgG-coated culture bottle and incubated for 1 h. The suspension was centrifuged at a low temperature for 8 min. Finally, the precipitant was cultivated in DMEM containing 10% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA), 100 U/mL penicillin and streptomycin, that was, primary rat alveolar epithelial cells.

Dex induction

Primary alveolar epithelial cells isolated from COPD rats were induced with 5 μM Dex or isodose normal saline for 3 days. Besides, primary alveolar epithelial cells isolated from SD rats were considered as control group.

Transfection

Cell suspension (1×10^5 /mL) was inoculated in a 6-well plate with 2 mL per well. After overnight culture, cells were transfected using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Culture medium was replaced at 6-8 h. At 48 h, culture medium containing 2 μg/mL puromycin was replaced for 72 h cultivation. Cells were passaged to a new 6-well plate for single clone growth within 1-2 weeks. Visible colonies were subjected to extended culture in a 96-well plate, 6-well plate and a culture bottle.

Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

Total RNAs were isolated from tissues using TRIzol (Invitrogen, Carlsbad, CA, USA). The concentration and purity of RNA were determined using an ultraviolet spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). After reverse transcription, complementary deoxyribose nucleic acids (cDNAs) were amplified for qRT-PCR at 94°C for 10 min, and 30 cycles at 94°C for 15 s and 60°C for 32 s. Relative mRNA level was calculated by $2^{-\Delta\Delta Ct}$. Primers were synthesized by XinFan Bio (Nanjing, China). Sequences of primers used for qRT-PCR were as follows: Human PACER: 5'-TGTAAATAGTTAATGTGAGCTCCACG-3' (forward) and 5'-GCAAATTCTGGCCATCGC-3' (reverse); Rat PACER: 5'-TCTGTACTGCGGGTGGAACA-3' (forward) and 5'-CAATTTGCCTGGTGAATGATTC-3' (reverse); Human β-actin: 5'-GTGAAGGTGACAGC AGTCGGTT-3' (forward) and 5'-GAAGTGGGGTGGTTTTAGGA-3' (reverse); Rat β-actin: 5'-TGTTACCAACTGG-

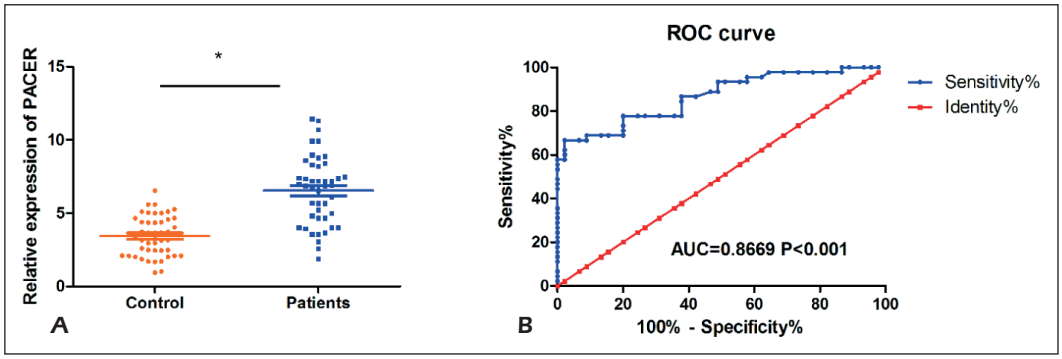

Figure 1. PACER triggered the development of COPD. **A**, Serum level of PACER in healthy controls and COPD patients. **B**, ROC curves depicted for the diagnostic potential of PACER in COPD (AUC=0.8669, $p<0.001$).

GACGACA-3' (forward) and 5'-GGGGTGTT-GAAGGTCTCAAA-3' (reverse).

Cell Counting Kit-8 (CCK-8)

1.0×10^3 cells were implanted in each well of a 6-well plate. 10 μL of CCK-8 solution was added (TaKaRa, Dalian, China). After 1-h culturing in the dark, the optical density at 450 nm was measured using a microplate reader.

Transwell Assay

100 μL of serum-free suspension (1.0×10^4 cells/mL) and 600 μL of serum-containing medium were applied to the top and bottom transwell chamber, respectively, and cultured overnight. Cells in the bottom were subjected to methanol fixation for 15 min, and crystal violet staining for 20 min. Migratory cells were counted in 5 randomly selected fields per sample.

Statistical Analysis

Data analysis was performed using Statistical Product and Service Solutions (SPSS) 20.0 software (SPSS Inc., Chicago, IL, USA). Differences between groups were compared using the Student's *t*-test. Receiver operating characteristic (ROC) method was introduced for assessing the diagnostic value of PACER in COPD. $p<0.05$ was considered statistically significant.

Results

PACER Triggered the Development of COPD

Compared with healthy subjects, serum level of PACER was higher in COPD patients (Figure 1A). Next, ROC curves were depicted based on the follow-up data of recruited COPD patients. The diagnostic potential of PACER in COPD was confirmed (AUC=0.8669, 95% CI=0.7993-0.9406, $p<0.001$) (Figure 1B). PACER may be a promising biomarker for COPD.

Pulmonary Functions in COPD Rats

After generating COPD model in rats, we evaluated their pulmonary functions. Compared with controls, lower TV, PEF, EF_{50}, $FEV_{0.3}$ and $FEV_{0.3}$/FVC were detected in COPD rats ($p<0.05$) (Table I). In addition, lower PaO_2 and higher $PaCO_2$ were recorded in COPD rats in comparison to controls ($p<0.05$) (Table II). It is suggested that pulmonary function was markedly declined in COPD rats.

Table I. Pulmonary functions in rats.

Pulmonary function	Control (n=10)	COPD (n=10)	*t*	*p*
TV (mL)	2.75±0.37	1.28±0.18	11.298	<0.001
PEF (mL/s)	37.26±2.33	15.98±1.58	23.904	<0.001
EF_{50} (mL/s)	1.92±0.57	1.33±0.25	2.998	0.008
$FEV_{0.3}$ (mL)	4.68±1.21	2.19±0.86	5.304	<0.001
$FEV_{0.3}$/FVC (%)	85.14±3.58	59.54±1.82	20.158	<0.001

TV, tidal volume; PEF, peak expiratory flow; EF_{50}, maximal expiratory flow in 50% vital capacity; $FEV_{0.3}$, forced expiratory volume in 0.3 second; $FEV_{0.3}$/FVC, forced expiratory volume in 0.3 second/forced vital capacity.

Table II. Arterial blood gas analysis in rats.

Arterial blood gas analysis	Control (n=10)	COPD (n=10)	*t*	*p*
PaO_2 (mmHg)	91.35±4.82	72.54±2.33	11.111	<0.001
$PaCO_2$ (mmHg)	45.21±5.07	58.91±5.82	5.613	<0.001

PaO_2, arterial partial pressure of oxygen; PaCO2, arterial partial pressure of carbon dioxide.

PACER Triggered Proliferative and Migratory Abilities in Pulmonary Alveolar Epithelial Cells Isolated from COPD Rats

In primary rat pulmonary alveolar epithelial cells, transfection of pcDNA-PACER markedly upregulated PACER, verifying a satisfactory transfection efficacy (Figure 2A). Overexpression of PACER enhanced viability and migratory cell number in primary rat pulmonary alveolar epithelial cells, suggesting the promotive proliferative and migratory abilities (Figure 2B, 2C).

Dex Induction Downregulated PACER and Attenuated Proliferative and Migratory Abilities in Pulmonary Alveolar Epithelial Cells Isolated from COPD Rats

Compared with pulmonary alveolar epithelial cells isolated from SD rats, PACER level was higher in those isolated from COPD rats, as well as proliferative and migratory potentials. After Dex induction in cells, PACER level was remarkably reduced (Figure 3A). Besides, viability and migratory cell number were reduced by Dex induction as well (Figure 3B, 3C).

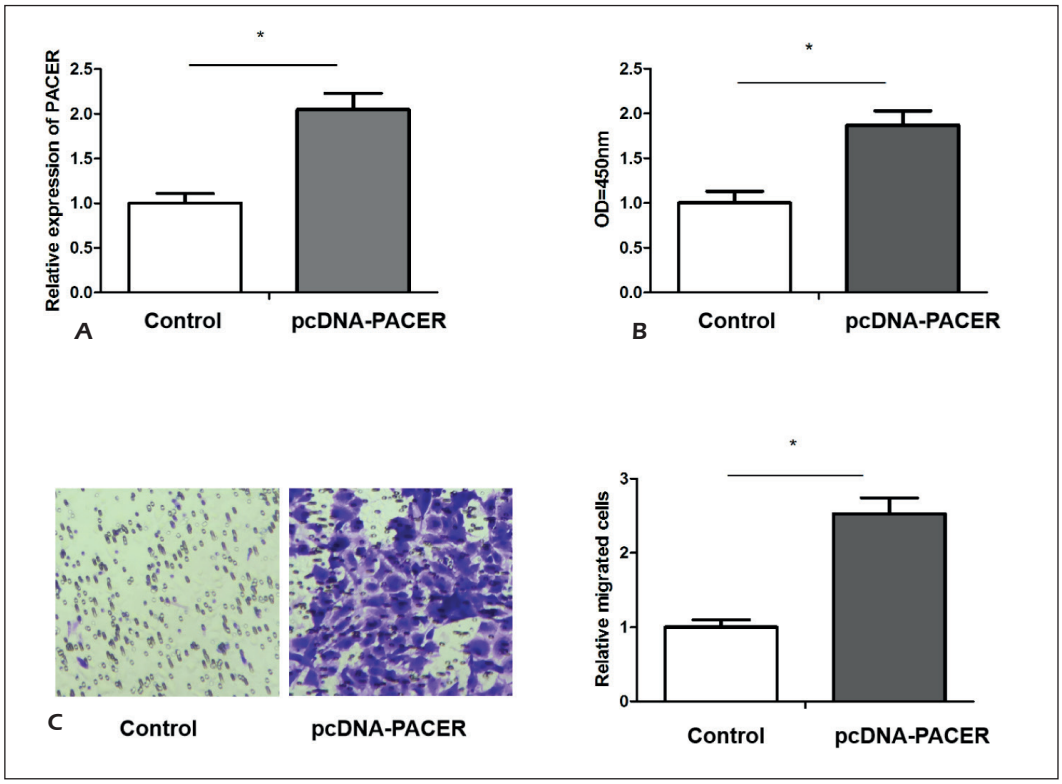

Figure 2. PACER triggered proliferative and migratory abilities in pulmonary alveolar epithelial cells isolated from COPD rats. **A**, Transfection efficacy of pcDNA-PACER in pulmonary alveolar epithelial cells. **B**, Viability in pulmonary alveolar epithelial cells transfected with pcDNA-NC or pcDNA-PACER. **C**, Migration in pulmonary alveolar epithelial cells transfected with pcDNA-NC or pcDNA-PACER (magnification: 40×).

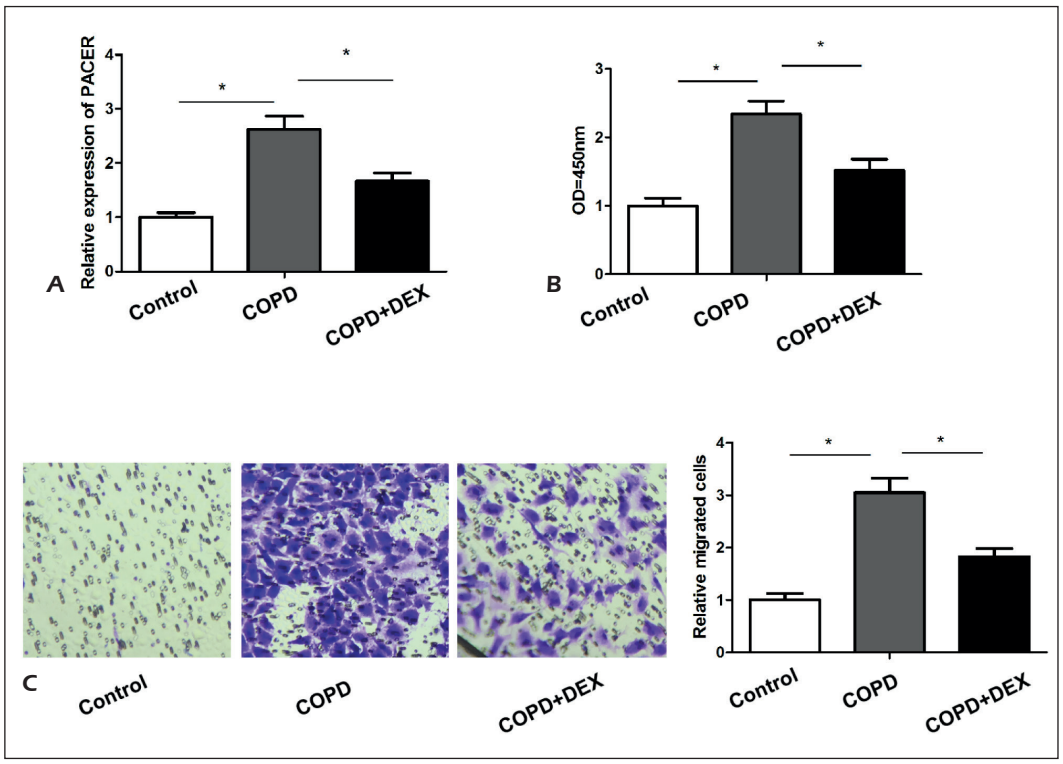

Figure 3. Dex induction downregulated PACER and attenuated proliferative and migratory abilities in pulmonary alveolar epithelial cells isolated from COPD rats. **A**, PACER level in pulmonary alveolar epithelial cells isolated from SD rats, and those isolated from COPD rats either treated with Dex or not. **B**, Viability in pulmonary alveolar epithelial cells isolated from SD rats, and those isolated from COPD rats either treated with Dex or not. **C**, Migration in pulmonary alveolar epithelial cells isolated from SD rats, and those isolated from COPD rats either treated with Dex or not (magnification: 40×).

PACER Regulated COPD by Targeting PP2A

Of note, viability and migratory cell number were lower in Dex-induced pulmonary alveolar epithelial cells isolated from COPD rats co-overexpressing with PACER and PP2A than those overexpressing PACER (Figure 4A, 4B). Therefore, PP2A was responsible for PACER-regulated phenotypes of pulmonary alveolar epithelial cells.

Discussion

As a chronic respiratory system disease, pulmonary infections and other factors can induce acute exacerbation of COPD, leading to a poor prognosis[17]. With the emergence of microarray analyses and high-throughput sequencing, detective ability of lncRNAs in the respiratory system has been largely improved. It is reported that LINC00882, LINC00883 and PVT1 are abnormally expressed in lung tissues of COPD patients[18]. Chen et al[19] demonstrated that lncRNA HCG4B is specifically expressed in COPD specimens, which may be a promising therapeutic target. LncRNA PACER has been identified to trigger the proliferative and metastatic capacities in osteosarcoma cells through activating COX-2. In addition, its expression is largely affected by DNA methylation[15]. Our results have shown that PACER was highly expressed in serum of COPD patients, and its diagnostic potential in COPD was confirmed by ROC method. Furthermore, PACER was found to drive the proliferative and migratory abilities in primary rat alveolar epithelial cells, thus aggravating COPD.

Dex is a highly selective α2 adrenergic receptor agonist, which is clinically used for sedation and anesthesia in acute exacerbation of COPD during mechanical ventilation[20]. The anti-inflammation, anti-oxidation and anti-apoptosis capacities of Dex in protecting lung diseases have been identified[21]. Li et al[22] suggested that Dex significantly decreases apoptotic rate in primary pulmonary alveolar epithelial cells isolated from COPD rats, displaying a protective effect. Consistently, our findings revealed that Dex induction markedly inhibited

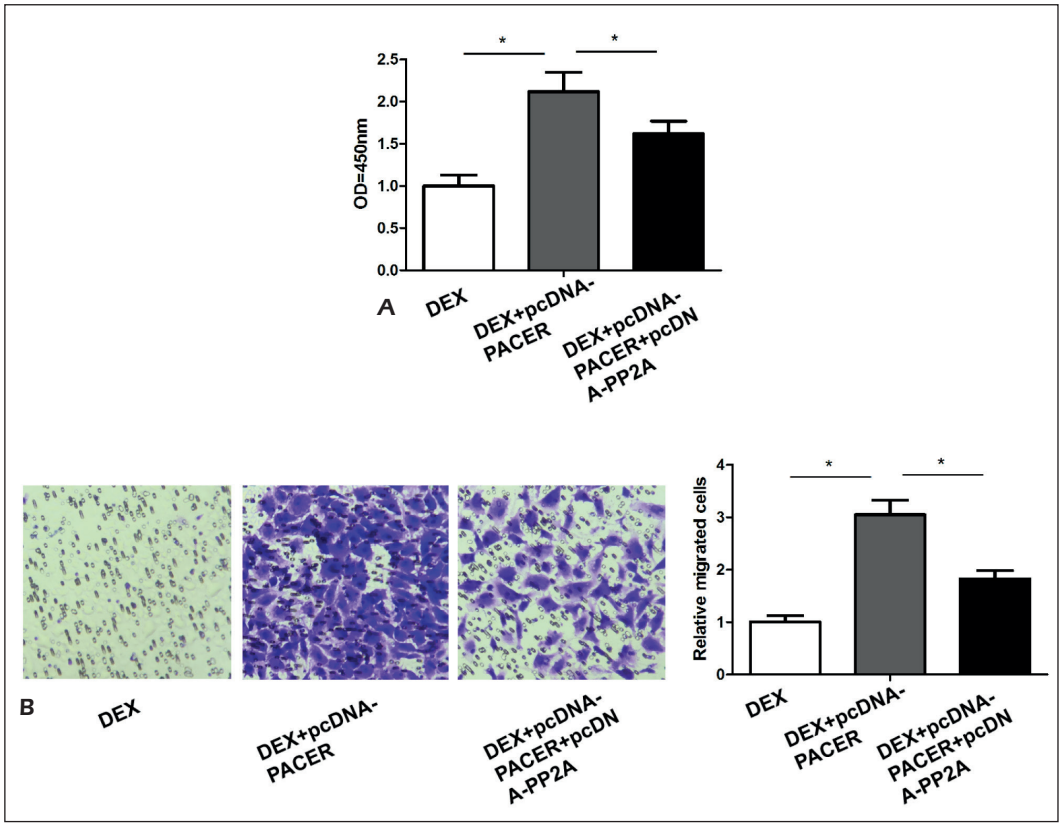

Figure 4. PACER regulated COPD by targeting PP2A. **A**, Viability in Dex-induced pulmonary alveo-lar epithelial cells isolated from COPD rats that were transfected with pcDNA-NC, pcDNA-PACER or pcDNA-PACER + pcDNA-PP2A. **B**, Migration in Dex-induced pulmonary alveolar epithelial cells isolated from COPD rats that were transfected with pcDNA-NC, pcDNA-PACER or pcDNA-PACER + pcDNA-PP2A (magnification: 40×).

proliferative and migratory abilities in primary pulmonary alveolar epithelial cells isolated from COPD rats. Zhou et al[23] proposed that through activating lncRNA CCAT1, Dex protects hepatocytes from oxygen/glucose deprivation-induced reperfusion injury. Here, through targeting PACER, Dex exerted its protective effect on COPD.

PP2A (protein phosphatase 2A) is the most critical serine/threonine protein phosphatase[24]. Neviani et al[25] pointed out that PP2A is lowly expressed in tumor stem cells of chronic myeloid leukocytes. Pharmacological activation of PP2A attenuates survival and self-renewal capacity of tumor stem cells at rest. Expression and activity of PP2A are reduced by respiratory syncytial virus and smoking exposure, which in turn drives the progression of COPD[26]. By targeting PP2A, lncRNA ASBEL serves as a vital regulator in the development of osteosarcoma, and it may be utilized as a therapeutic target[27]. In our study, PP2A level was downregulated by PACER, and thus participated in the regulation of pulmonary alveolar epithelial cells. To sum up, Dex effectively inhibits PACER-induced proliferation and migration in pulmonary alveolar epithelial cells *via* targeting PP2A, thereby protecting lung tissues against COPD. This study guides a novel direction for diagnosis, treatment and monitoring COPD, which lays a solid foundation for developing the targeted therapy of COPD.

Conclusions

PACER drives the proliferative and migratory abilities of alveolar epithelial cells through activating PP2A. Dexmedetomidine is conducive to COPD treatment by downregulating PACER

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Conflict of Interests

The authors declare that they have no conflict of interest.

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