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Original Article

Transcription Factor PU.1 Inhibits *Aspergillus fumigatus* Infection via Surfactant Protein-D

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Aspergillosis is a life-threatening disease in individuals with compromised immune systems. Fungal invasion is a highly critical process during host cellular infection. Several papers have reported that transcription factors are responsible for the infection process. To investigate what transcription factors are involved in the process in an effort to inhibit fungal infection into cells, I checked the surfactant protein family and PU.1 transcription factor levels in A549 cells infected with *A. fumigatus* conidia. PU.1 and surfactant protein-D levels were reduced in cells infected with fungal conidia. I then observed an increase in surfactant protein-D on PU.1-overexpressed cells. Infection of *A. fumigatus* conidia was decreased in PU.1-overexpressed cells, whereas the suppression of PU.1 did not lead to any changes in cases of *A. fumigatus* conidia infection. These results indicate that PU.1 inhibits the infection of *A. fumigatus* conidia via the expression of surfactant protein-D, suggesting that PU.1 is a key transcription factor for protection against *A. fumigatus* invasion.

Key Words: Aspergillosis, *Aspergillus fumigatus*, PU.1, Surfactant Protein-D

INTRODUCTION

Invasive aspergillosis is a life-threatening pulmonary or systemic infection. Invasion of *Aspergillus fumigatus* (*A. fumigatus*) is the main cause of *Aspergillus* infection in humans (Segal, 2009; Sharon et al., 2011). *A. fumigatus* is classified as a group of opportunistic pathogens which exist ubiquitously in the natural environment (Segal, 2009). Depending on the health condition of the infected human, *Aspergillus* species can cause diseases ranging from local allergic reactions to invasive infections or even pneumonia (Barnes and Marr, 2006).

Surfactant proteins play a key role in the host defense mechanism. Pulmonary surfactant proteins are located on lung alveolar surfaces and consist of phospholipids and proteins (Whitsett and Weaver, 2002). Surfactant proteins are made by alveolar type II cells and Clara cells, the major seed cells of peripheral airway cells. Surfactant proteins have several functions; they reduce tension to prevent an alveolar collapse, prevent pathogens from spreading, and regulate immune reactions (Wright, 2005).

Pulmonary surfactant proteins (SP) are divided into two groups: hydrophobic surfactant proteins (SP-A and SP-B) and hydrophilic surfactant proteins (SP-C and SP-D). SP-B proteins regulate lung injuries during inflammation induced by the IgG immune complex (Yan et al., 2012). The SP-C type interacts with lipopolysaccharides and decreases the cytokine activity of macrophages (Augusto et al., 2003). SP-A and SP-D, as innate immune proteins, have been dem-

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onstrated to be antibacterial (LeVine et al., 1998) and antifungal (McCormack et al., 2003). The expression of SP genes is regulated by several nuclear proteins, including thyroid transcription factor-1 (TTF-1) and hepatocyte nuclear factor-3β (HNF-3β) (Zhou et al., 1996).

The transcription factor PU.1 is a member of the E-twenty-six family and is readily found in myeloid cells. PU.1 can increase the activation of the eosinophil granule gene, induce histone modification in dendritic cells, and increase IL-4 production in mast cells (Henkel and Brown, 1994; Gombart et al., 2003). In macrophages, PU.1 has an important role in differentiation processes (Lawrence and Natoli, 2011), and PU.1 induces lung inflammation in neutrophils by regulating the cell signaling process (Karpurapu et al., 2011). Moreover, the regulation of PU.1 expression may be a good therapeutic target for disease control during inflammation of the asthmatic airway (Qian et al., 2015).

In the present study, I used *A. fumigatus* conidia to demon strate the cellular response at the transcription level in human lung epithelial cells (A549). This study can provide a better understanding of the invasion processes occurring at the molecular level, and the findings imply that transcription factor PU.1 is a viable therapeutic agent for the treatment of a variety of fungal infections.

MATERIAL AND METHODS

A. fumigatus strain and culture conditions

A. fumigatus AF293 (wild type; WT) strains were used. A glucose-minimal medium with 0.1% (w/v) of yeast extract (MMY) along with supplements was used for the general culture of the fungal strains (Kafer, 1977). Amounts of 5×10^5 conidia /mL were inoculated on solid MMY and incubated at 37℃ for 3~4 days. *A. fumigatus* conidia were detached from agar plates. They were suspended in sterile ultrapure H_2O with 0.02% Tween 80. The resting conidia were washed two times and counted with a hemocytometer, after which they were stored at 4℃ until use (up to 48 h). A549 cells from the human lung epithelial cell line were cultured in RPMI 1640 with 10% fetal bovine serum (Hyclone, USA), 100 mg/L streptomycin, and 16 mg/L penicillin at 37℃ in 5% CO_2. The A549 cells were seeded into 24-well plates with 1×10^5/wells and cultured in RPMI 1640 with 10% FBS for 16 h to 18 h before being infected with conidia.

Establishment of an *in vitro* infection model

Following the incubation process, an amount of 1×10^4 conidia was added to each well in each experimental group, with the wells then incubated for 6 h at 37℃. The cells were washed five times with PBS to remove unattached conidia. Amounts of five hundred microliters of RIPA buffer (iNtRON, Seoul, Korea) were added to the wells to disrupt the cells membrane and release the intracellular conidia. Lysates (50 μL) was incubated on potato-dextrose agar plates for 36 h at 37℃. The invasiveness of the conidia was calculated using the following formula: mean of colony-forming units × 1000/50.

Cloning of PU.1 and transfection

Total RNA was isolated from 1×10^6 A549 cells using Easy-Spin™ Total RNA extraction kits with DNase I (iNtRON, Korea) following the manufacturer's protocol. RT-PCR was performed using a One-Step RT-PCR kit (QIAGEN, Valencia, CA, USA). The primers used were 5'-GAA TTC AGG CGT GCA AAA TGG AAG GG-3' (sense) and 5'-CTC GAG TCA GTG GGG CGG GTG GCG CC-3' (antisense). I transfected the plasmid into the cells with Lipofectamine®2000 (Invitrogen, Carlsbad, CA, USA). For each transfection, I used pcDNA3.1-PU.1 or 2 μL of a siRNA duplex (SC-36330, Santa Cruz Biotech, TX, USA) into 100 μL of the transfection medium.

qRT-PCR

Total RNA (2 μg in a total volume of 20 μL) was used for reverse transcription. Quantitative RT-PCR was performed according to the manufacturer's instructions (Qiagen, USA) using a Rotor-Gene Q device (Qiagen, USA). Each run was assayed three times with 2× qPCR SYBR Green Mix kits (Doctor Protein, Korea) and 100 mM of each primer. Primers sets (Table 1) were used to detect SP-A, SP-B, SP-C, SP-D (Che et al., 2012), PU.1 and β-actin (Kim et al., 2008).

The one-step qRT-PCR conditions were as follows: 42℃ (40 min) for reverse transcription and 95℃ (15 min) for one cycle, followed by 95℃ (30 s) and 55℃ (30 s) for 40

Table 1. List of the Sequences of Primers for RT-PCR

Genes		Sequences (5' → 3')
SP-A	Sense	5'-CTG TCC CAA GGA ATC CAG AG-3'
	Anti-sense	5'-CCG TCT GAG TAG CGG AAG TC-3'
SP-B	Sense	5'-CAC CAT GTT CCC CAT TCC TCT-3'
	Anti-sense	5'-TCA TCC ATG GAG CAC CGG AGG ACG-3'
SP-C	Sense	5'-CTG GTT ACC ACT GCC ACC TT-3'
	Anti-sense	5'-TCA AGA CTG GGG ATG CTC TC-3'
SP-D	Sense	5'-AGG AGC AAA GGG AGA AAG TGG G-3'
	Anti-sense	5'-CAG CTG TGC CTC CGT AAA TGG-3'
PU.1	Sense	5′-CAG CTC AGA TGA GGA G-3′
	Anti-sense	5′-CTT GGA CGA GAA CTG GAA G-3’
β-actin	Sense	5'-GCC AAC ACA GTG CTG TCT GG-3'
	Anti-sense	5'-TAC TCC TGC TTG CTG ATC CA-3'

cycles. Amplification of the target DNA was checked by means of a melting curve analysis from 55℃ to 95℃ (+0.5℃ ramping for 10 s). I analyzed the data using the Ct method to calculate the ratio between the experimental group and the control group. To verify the contamination of the DNA, I used the sample without primers as a negative control. Three independent biological replicates were carried out.

RESULTS

The surfactant protein family, SP-C and SP-D, were suppressed in *A. fumigatus* conidia-infected A549 cells

The function of the SP family in the pathogenesis of *A. fumigatus* infection is controversial. To investigate the role of surfactant proteins in a fungal infection, I examined the surfactant protein family expression levels in *A. fumigatus* conidia-infected A549 cells. After the incubation and isolation of RNA in conidia-infected cells, I ran qRT-PCR assays to determine the SP family transcript expression level.

The conidia infection of *A. fumigatus* caused the suppression of SP-C and SP-D expression levels in the surfactant protein family. In addition, the results showed that SP-D responded to the conidia concentration when the exposure level was high (10^7 cells) (Fig. 1). I also found that the surfactant protein responds to the amount of *A. fumigatus* conidia in a dose-dependent manner. Thus, my result suggests that the SP-D gene expression level is suppressed by the direct infection of *A. fumigatus* conidia.

PU.1 mRNA is also suppressed in *A. fumigatus* conidia-infected A549 cells

The potential role of PU.1 in the pathogenesis of an infection of *A. fumigatus* remains unknown. To investigate the significance of PU.1 during the infection process, I assessed its expression level in *A. fumigatus* conidia-infected cells.

When I induced the suppression of SP-D in conidia-infected cells, I found that PU.1 mRNA was also suppressed (Fig. 2). This result provides evidence that the infection of *A. fumigatus* conidia leads to the down-regulation of PU.1 in cells.

SP-D expression is increased in PU.1-transfected cells

I have shown that SP-D and PU.1 are suppressed in cells infected with *A. fumigatus* conidia. However, research has not demonstrated the function of PU.1 as a regulator of SP-D expression. I investigated whether PU.1 has a role in increasing SP-D expression levels. I transfected the PU.1 expression vector (1 μg/μL) transiently (Fig. 3A) and checked the SP expression levels in cells by means of qRT-PCR assays. When PU.1 was over-expressed in A549 cells, only SP-D was increased in the cells (Fig. 3B). I therefore found

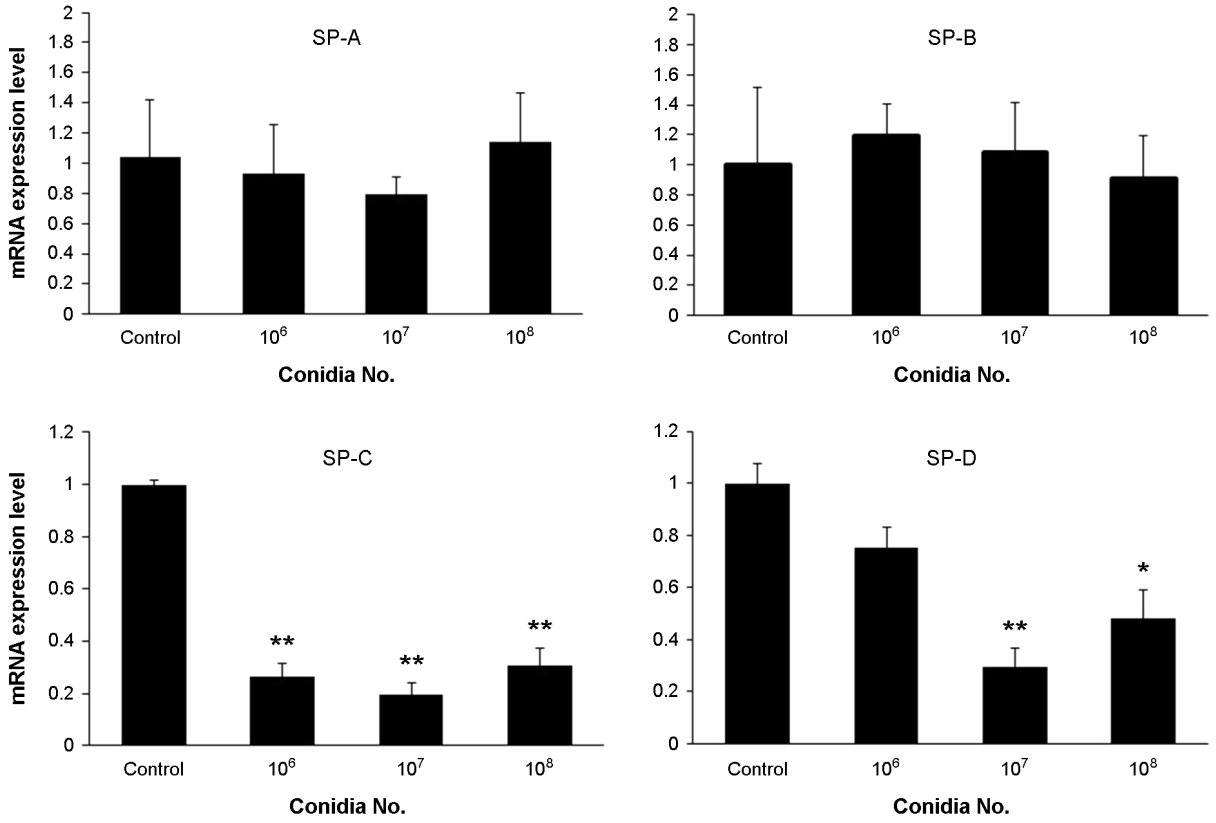

Fig. 1. Effects of the number of conidia on surfactant protein mRNA expression levels in human A549 cells. Relative mRNA expression of surfactant protein family members of *A. fumigatus*-infected cells. $*P < 0.05$ and $**P < 0.01$.

that PU.1 serves as a positive regulator of the SP-D expression levels in this case.

A. fumigatus invasion is decreased in PU.1 transfected A549 cells

Mice lacking SP-D are protected during an infection of *Cryptococcus neoformans* (*C. neoformans*), whereas the increased SP-D enhances *C. neoformans* growth in organs (Geunes-Boyer et al., 2012). I sought to determine how the increased SP-D level through PU.1 activity influences an *A. fumigatus* conidia infection. To address the role of PU.1 during the infection process of *A. fumigatus* conidia, I transiently transfected the PU.1 expression vector into A549 cells and infected the cells with *A. fumigatus* conidia. In addition, I checked whether the SP-D expression level was increased by PU.1 transfection. My findings showed that the invasion of *A. fumigatus* was inhibited in cells transfected

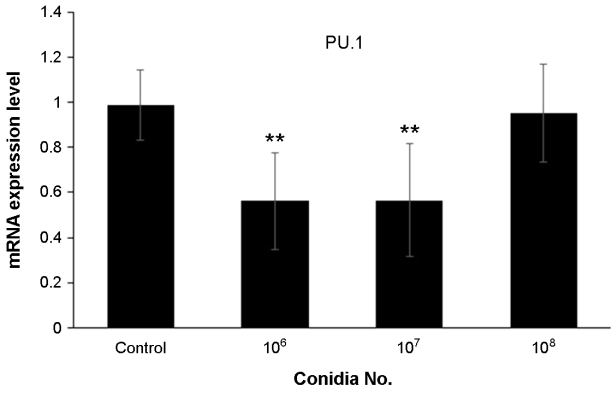

Fig. 2. mRNA expression of PU.1 in *A. fumigatus*-infected cells. Significance was determined by Student's *t*-tests. $**P < 0.01$.

by a relatively high concentration (8 μg) of PU.1 (Fig. 4).

One question is whether the infection of *A. fumigatus* conidia is increased in SP-D-suppressed cells when the PU.1

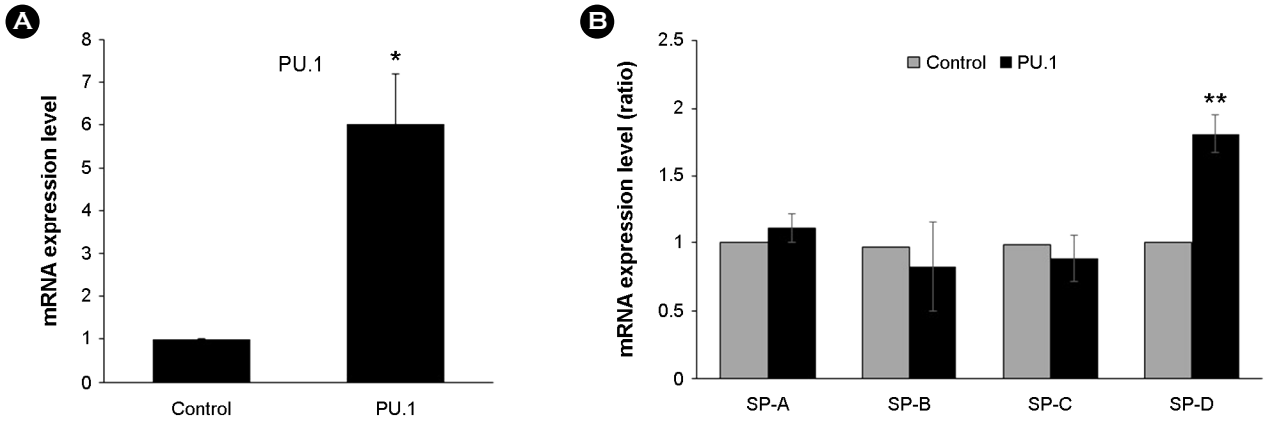

Fig. 3. Effects of PU.1 on surfactant protein mRNA expression levels in human A549 cells: (A) PU.1 mRNA expression level for PU.1-transfected cells. (B) mRNA expression level of members of the surfactant protein family in PU.1-transfected cells. *$P < 0.05$, **$P < 0.01$.

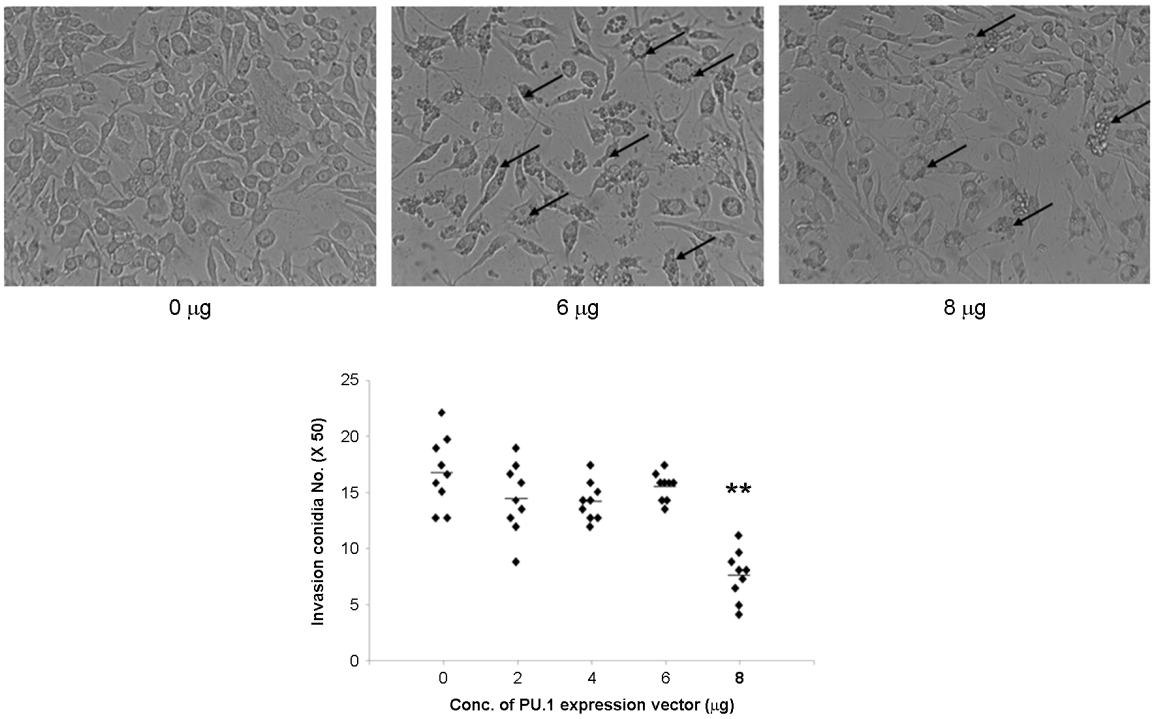

Fig. 4. Effects of the PU.1 concentration on instances of *A. fumigatus* conidia invasion in human A549 cells. Significance was determined by Student's *t*-tests, with **$P < 0.01$.

function is suppressed with its siRNA, leading to decreased SP-D levels.

Although PU.1 (Fig. 5A) and SP-D (Fig. 5B) were suppressed in cells treated with siRNA against PU.1, I observed that the invasion of *A. fumigatus* conidia did not increase in the PU.1-suppressed condition (Fig. 5C).

I summarized that *A. fumigatus* conidia readily induced the suppression of PU.1 and the SP-D expression level for infection and that PU.1 functions to protect cells from *A. fumigatus* conidia during an infection.

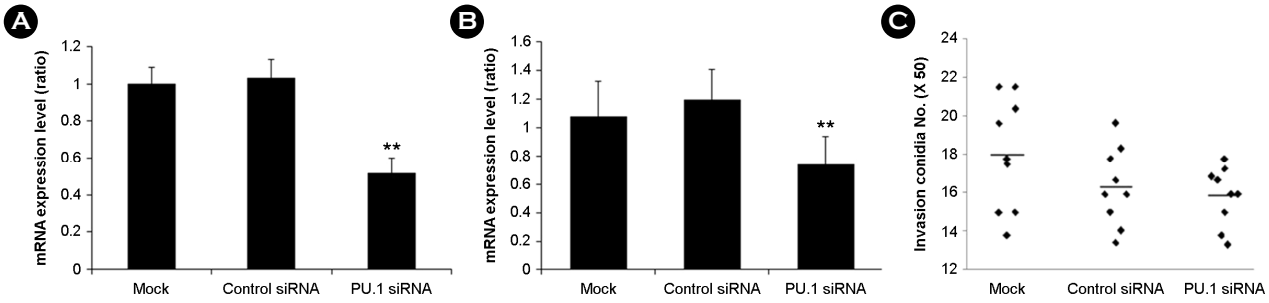

Fig. 5. Effects of PU.1 siRNA on human A549 cells: (A) mRNA expression level of PU.1 from PU.1 siRNA-treated cells. (B) mRNA expression level of SP-D in PU.1 siRNA-treated cells. (C) Invasion assay of *A. fumigatus* on PU.1 siRNA-treated cells. $^{**}P < 0.01$.

DISCUSSION

Aspergillosis represents a severe threat to immunosuppressed individuals; hence, developing a new therapeutic roadmap will help defend them and improve their clinical outcomes. My study found that PU.1 is a positive regulator of the expression of SP-D in *A. fumigatus* conidia-infected cells. Moreover, infections of *A. fumigatus* conidia are decreased in SP-D overexpressed cells.

SP-D has several functions in the regulation of the innate immune response in the lung (Wright, 2005). For example, SP-D suppresses the dissemination of infectious microbes by inhibiting their behaviors by, for example, agglutination and growth suppression (Wu et al., 2003). Moreover, SP-D enhances the elimination of microbes by assisting with the phagocytosis of macrophages. SP-D also interacts with pattern-recognition receptors such as toll-like receptors CD14 and MD-2 and thus regulates inflammatory responses (Ohya et al., 2006). Additionally, SP-D has been used to induce various cytokines and chemokines in an effort to increase the clearance of bacterial, viral, and fungal pathogens. The protective roles of SP-D during bacterial and viral infections have been thoroughly investigated (Giannoni et al., 2006). However, its expression mechanism during infections of fungi has not been characterized as well, though many fungal studies have been conducted with *A. fumigatus*.

Inflammation induced by *A. fumigatus* is related to increased SP-D protein expression levels (Haczku et al., 2001). However, my data demonstrated that SP-C and SP-D in the SP family are only suppressed in conidia-infected cells and that they respond in a dose-dependent manner. I found that SP-D expression levels in infected cells are increased to protect the cells.

Serum SP-D levels in allergic patients, those with hypersensitive lung disease, and asthmatics have been found to be increased upon medical diagnosis and decreased following corticosteroid therapy (Tanaka et al., 2000). Patients with idiopathic pulmonary fibrosis have high blood SP-D levels, and high SP-D levels are detected in the blood in those with interstitial pneumonia during collagen vascular disease and pulmonary alveolar proteinosis (Takahashi et al., 2000).

PU.1 is a well-known principal transcriptional regulator of innate immunity. PU.1 is decreased significantly in monocytes infected with *Ehrlichia chaffeensis* (Lin and Rikihisa, 2004). However, in human monocyte leukemia cells infected with *A. fumigatus* conidia, the protein expression level, not the mRNA, of PU.1 is increased (Wang et al., 2016). My results here showed that PU.1 is also suppressed in *A. fumigatus* conidia-infected cells. When I increased the PU.1 expression level, there was a significant decrease in conidia invasion into the cells. NFATc3 and TTF-1 directly interact with each other and synergistically activate SP-D expression during the transcription processes (Dave et al., 2004). C/EBP elements can also modulate the promoter activity of SP-D with interactions in the near-distal promoter region (He and Crouch, 2002). AP-1 proteins modulate SP-D gene expression levels in pulmonary epithelial cells during transcriptional activity (He et al., 2000). However, I did not observe any increase in infected conidia in A549 cells transfected with siRNA specific to PU.1.

This study suggests that PU.1 serves as a positive regulator of SP-D expression as a transcription factor and that the increased amount of SP-D protects cells from *A. fumigatus* infection. The findings here clearly indicate that transcription factor PU.1 is a good regulator during an *A. fumigatus* conidia infection via SP-D and that it is a potential candidate for use in aspergillosis treatments.

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CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest to disclose.

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