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T-plastin contributes to epithelial-mesenchymal transition in human lung cancer cells through FAK/AKT/Slug axis signaling pathway

Soon Yong Park[1,2,#], Hyeongrok Choi[2,#], Soo Min Choi[2], Seungwon Wang[2], Sangin Shim[3], Woojin Jun[4], Jungkwan Lee[5] & Jin Woong Chung[2,]*

[1]Research Center, Dongnam Institute of Radiological & Medical Sciences, Busan 46033, [2]Department of Biomedical Sciences, Dong-A University, Busan 49315, [3]Department of Agronomy, Gyeongsang National University, Jinju 52828, [4]Department of Food and Nutrition, Chonnam National University, Gwangju 61186, [5]Department of Applied Biology, Dong-A University, Busan 49315, Korea

T-plastin (PLST), a member of the actin-bundling protein family, plays crucial roles in cytoskeletal structure, regulation, and motility. Studies have shown that the plastin family is associated with the malignant characteristics of cancer, such as circulating tumor cells and metastasis, by inducing epithelial-mesenchymal transition (EMT) in various cancer cells. However, the role of PLST in the EMT of human lung cancer cells remains unclear. In this study, we observed that PLST overexpression enhanced cell migratory and invasive abilities, whereas its downregulation resulted in their suppression. Moreover, PLST expression levels were associated with the expression patterns of EMT markers, including E-cadherin, vimentin, and Slug. Furthermore, the phosphorylation levels of focal adhesion kinase (FAK) and AKT serine/threonine kinase (AKT) were dependent on PLST expression levels. These findings indicate that PLST induces the migration and invasion of human lung cancer cells by promoting Slug-mediated EMT via the FAK/AKT signaling pathway. [BMB Reports 2024; 57(6): 305-310]

INTRODUCTION

Lung cancer is one of the most common malignant cancers worldwide, accounting for 20% of cancer-related deaths (1). Non-small cell lung cancer (NSCLC) is the predominant type of lung cancer. Due to the difficulty of early diagnosis, it is often diagnosed after metastasis has occurred, leading to a poor prognosis (2-4). According to previous studies, NSCLCs acquire invasive properties and progress to metastasis through epithelial-mesenchymal transition (EMT) (5). Therefore, investigating the underlying EMT mechanism and associated factors of NSCLCs is necessary for its early diagnosis and development of therapeutic strategies.

EMT is a process by which adhesive epithelial cells transform into migratory and invasive mesenchymal phenotypes (6). EMT is essential for organ development and tissue wound healing under normal conditions. However, it strongly promotes metastasis by enhancing cell motility in cancers (7, 8). Specifically, lung cancer can easily spread to other organs such as other parts of the lungs, the brain, the liver, bones, and nearby lymph nodes (9, 10). EMT generally requires cytoskeletal changes through the regulation of polarity by controlling actin filaments, keratin, vimentin, and alpha-smooth muscle actin to facilitate migratory abilities (11-13), emphasizing the importance of verifying the cellular cytoskeletal regulatory factors that promote EMT to understand the mechanisms that can inhibit it.

T-plastin (PLST), also known as plastin 3, is a member of the actin-bundling protein family and is expressed in almost all cell types (14). PLST is associated with the actin cytoskeleton and is involved in cell motility (15). In previous studies, PLST was found to be overexpressed in circulating tumor cells (CTCs) of breast and prostate tumors, indicating its potential as a novel biomarker for CTCs (16, 17). Although PLST expression is associated with the promotion of EMT in gastric and colorectal cancer cells (18, 19), the association between PLST and EMT in lung cancer remains unclear.

Here, we demonstrate that PLST expression is associated with EMT progression in H460 and H1299 human lung cancer cells. PLST overexpression induced mesenchymal phenotypes, including changes in the expression pattern of EMT-related genes, and enhanced migratory and invasive abilities through the focal adhesion kinase (FAK)/AKT serine/threonine kinase (AKT) signaling pathway, whereas PLST downregulation resulted in the opposite phenotypes. These results suggested that PLST induced the migration and invasion of H460 and H1299 human

*Corresponding author. Tel: +82-51-200-7270; Fax: +82-51-200-7269; E-mail: jwchung@dau.ac.kr
#These authors contributed equally to this work.

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lung cancer cells by triggering EMT via the FAK/AKT axis.

RESULTS

Upregulation of PLST promotes cell migration, invasion, and mesenchymal-like morphological change in human lung cancer cells

To investigate the effect of PLST overexpression on the motility of H460 and H1299 human lung cancer cells, we transfected the cells with an empty vector (EV) as a control or a PLST overexpression vector (PLST OV). Subsequently, we confirmed the overexpression of PLST mRNA and proteins (Fig. 1A, B). We performed a wound-healing assay to examine the changes in cell migratory ability resulting from PLST overexpression in H460 and H1299 human lung cancer cells. The wound-healing ability of H460 and H1299 cells overexpressing PLST was higher than that of control cells (Fig. 1C). Additionally, cells were seeded onto collagen- or Matrigel-coated 8-μm-pore membranes to measure their migratory and invasive abilities. Simi-

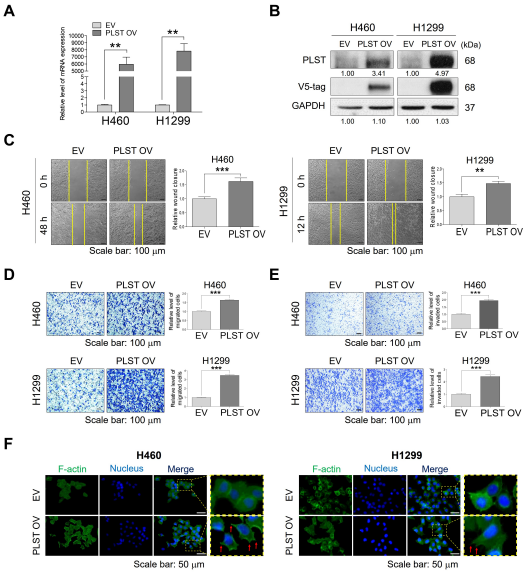

Fig. 1. Effects of PLST upregulation on cell migration, invasion and morphological changes in H460 and H1299 cells. (A) The cells were transfected with EV or PLST OV, which is based on pcDNA6/V5-His B plasmid vector, using Lipofectamin™ 3000 reagent. Then, qRT-PCR was performed to examine the mRNA expression level of PLST. (B) Western blotting analysis was performed to examine the protein expression level of PLST. V5 was used as a protein tag of exogenous PLST. (C) Wound healing assay was performed to measure migratory ability by PLST overexpression in H460 and H1299 cells. Wound healing process was observed using a microscope. Quantitative analysis of increase in wound-healing ability by PLST overexpression in H460 and H1299 cells. Scale bar: 100 μm. (D) Cell migration assay was performed to examine cell migratory ability by PLST overexpression using a Boyden chamber in H460 and H1299 cells. The migrated cells on the bottom surface of membrane were observed using a microscope. Quantitative analysis of increase of migrated cell number by PLST overexpression in H460 and H1299 cells. Scale bar: 100 μm. (E) Cell invasion assay was performed to determine cell invasive ability by PLST overexpression using a Boyden chamber in H460 and H1299 cells. The invaded cells on the bottom surface of membrane were observed using a microscope. Quantitative analysis of increase of invaded cell number by PLST overexpression in H460 and H1299 cells. Scale bar: 100 μm. (F) F-actin staining assay was performed to examine the cell morphological change of H460 and H1299 cells by PLST overexpression. Scale bar: 50 μm. These results are the average of three independent experiments. Data are represented as mean ± SD (**P < 0.01; ***P < 0.001).

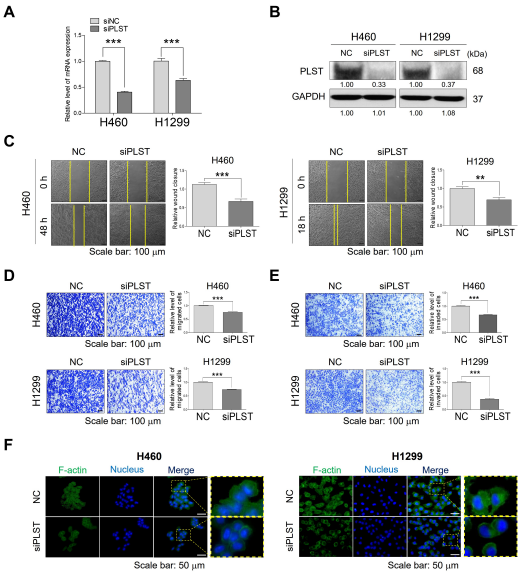

Fig. 2. Effects of PLST downregulation on cell migration, invasion and morphological changes in H460 and H1299 cells. (A) The cells were transfected with 10 nM NC siRNA or 100 nM PLST siRNA using Lipofectamin™ 3000 reagent. Then, qRT-PCR was performed to substantiate the mRNA expression level of PLST. (B) Western blotting analysis was performed to substantiate the protein expression level of PLST. (C) Wound healing assay was performed to measure migratory ability by PLST knockdown in H460 and H1299 cells. Wound healing process was observed using a microscope. Quantitative analysis of decrease in wound-healing ability by PLST knockdown in H460 and H1299 cells. Scale bar: 100 μm. (D) Cell migration assay was performed to examine cell migratory ability by PLST knockdown using a Boyden chamber in H460 and H1299 cells. The migrated cells on the bottom surface of membrane were observed using a microscope. Quantitative analysis of decrease of migrated cell number by PLST knockdown in H460 and H1299 cells. Scale bar: 100 μm. (E) Cell invasion assay was performed to determine cell invasive ability by PLST knockdown using a Boyden chamber in H460 and H1299 cells. The invaded cells on the bottom surface of membrane were observed using a microscope. Quantitative analysis of decrease of invaded cell number by PLST overexpression in H460 and H1299 cells. Scale bar: 100 μm. (F) F-actin staining assay was performed to examine the cell morphological change of H460 and H1299 cells by PLST knockdown. Scale bar: 50 μm. These results are the average of three independent experiments. Data are represented as mean ± SD (**P < 0.01; ***P < 0.001).

larly, PLST overexpression promoted the migratory and invasive abilities of H460 and H1299 cells (Fig. 1D, E). Next, to investigate whether the increase in migratory and invasive abilities due to PLST overexpression was dependent on morphological changes, we stained F-actin with phalloidin. Surprisingly, PLST overexpression induced a spindle-shaped morphology in both H460 and H1299 cells (Fig. 1F), indicating that PLST promotes the mesenchymal morphological phenotype and enhances the motility of lung cancer cells.

Downregulation of PLST represses cell migration, invasion and mesenchymal-like morphological change in human lung cancer cells

To investigate whether PLST downregulation suppresses cell motility, we performed experiments to downregulate PLST using negative control (NC) or PLST small interfering RNA (siPLST) treatment. Subsequently, we confirmed the decreased mRNA and protein expression levels (Fig. 2A, B). For validation, we performed experiments following the same steps as those shown in Fig. 1. Remarkably, the wound-healing ability of H460 and H1299 cells was decreased by PLST downregulation (Fig. 2C). Moreover, the cell migration and invasion assays showed that PLST downregulation diminished the migratory and invasive abilities of H460 and H1299 cells (Fig. 2D, E). In addition, PLST downregulation induced morphological changes, suppressing the mesenchymal shape (Fig. 2F). These results suggest that PLST suppression represses the mesenchymal morphological phenotype and attenuates the motility of lung cancer cells.

PLST induces Slug expression in human lung cancer cells

To further investigate the molecular mechanism underlying the relationship between PLST and cell motility, we screened the mRNA levels of EMT markers, including Snail, Slug, Twist, and vimentin as mesenchymal markers, and E-cadherin as an epithelial marker. PLST overexpression showed significant results, indicating an increase in Slug, Twist, and vimentin and a decrease in E-cadherin mRNA expression levels in H460 and H1299 cells (Fig. 3A). Conversely, PLST downregulation demonstrated significant results, showing a decrease in Slug and vimentin and an increase in E-cadherin mRNA expression levels (Fig. 3B). Among these genes, changes in the expression of Slug, a mesenchymal marker highly associated with cancer progression, malignancy, and metastasis, were the most prominent. Therefore, we inserted the Slug promoter sequence into a luciferase vector and measured Slug gene expression following PLST overexpression or downregulation. The results showed that Slug expression varied depending on the level of PLST expression (Fig. 3C). Next, we performed western blotting to validate changes in the expression of Slug, vimentin, and E-cadherin according to the level of PLST expression. Similar to the mRNA levels, PLST overexpression resulted in increased expression of Slug and vimentin and decreased expression of E-cadherin, whereas PLST downregulation showed the opposite pattern of results (Fig. 3D, E). Furthermore, PLST-regulated

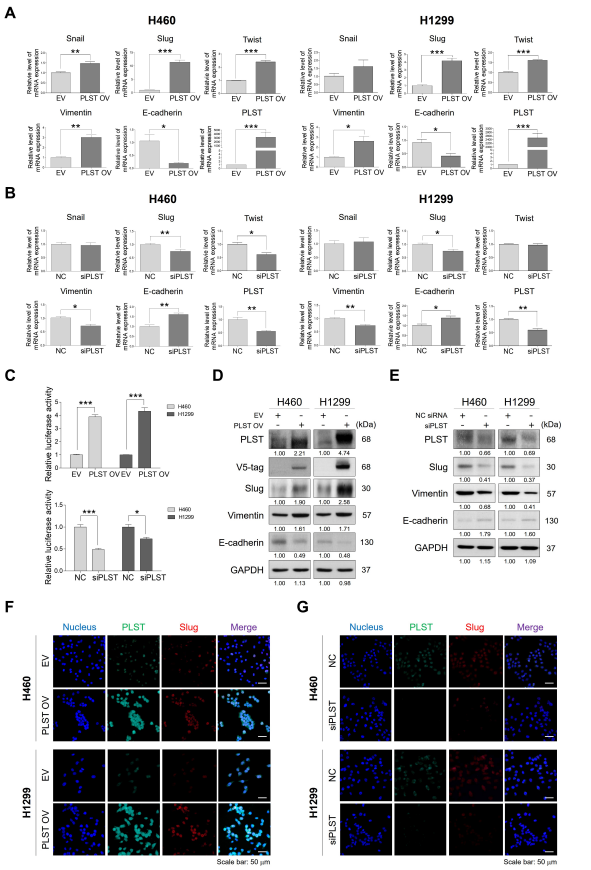

Fig. 3. The promotion of EMT through PLST-induced Slug expression in H460 and H1299 cells. (A) qRT-PCR was performed to measure the mRNA levels of Snail, Slug, Twist, vimentin and E-cadherin by PLST overexpression in H460 and H1299 cells. (B) qRT-PCR was performed to measure the mRNA levels of Snail, Slug, Twist, vimentin and E-cadherin by PLST knockdown in H460 and H1299 cells. (C) Luciferase assay was performed to measure the change of Slug promoter activity (firefly/renilla) by PLST overexpression or knockdown. (D) Western blotting analysis was performed to confirm the protein expression level changes of Slug, E-cadherin and vimentin by PLST overexpression in H460 and H1299 cells. (E) Western blotting analysis was performed to confirm the protein expression level changes of Slug, vimentin and E-cadherin by PLST knockdown in H460 and H1299 cells. (F) Immunofluorescence analysis was performed to examine the protein expression of Slug in cellular level by PLST overexpression in H460 and H1299 cells. Scale bar: 50 μm. (G) Immunofluorescence analysis was performed to examine the protein expression of Slug in cellular level by PLST knockdown in H460 and H1299 cells. Scale bar: 50 μm. These results are the average of three independent experiments. Data are represented as mean ± SD (*P < 0.05; **P < 0.01; ***P < 0.001).

Slug expression levels were examined by immunofluorescence analysis. The expression levels of Slug in H460 and H1299 cells were significantly dependent on the level of PLST expression at the cellular level (Fig. 3F, G). These results suggest that Slug expression is regulated by PLST expression. Taken

together, PLST may promote EMT through the regulation of Slug, vimentin, and E-cadherin.

PLST promotes EMT via FAK/AKT/Slug signaling axis pathway in human lung cancer cells

We focused on the FAK signaling pathway, a key regulator of cell motility and morphology, because FAK is known to promote cell motility and EMT (20, 21). Additionally, FAK is associated with plastin 2, also known as lymphocyte cytosolic protein-1 (LCP1), which is a member of the plastin family (22). We confirmed that PLST overexpression enhanced the phosphorylation levels of FAK and AKT. Furthermore, this enhancement was blocked by the FAK inhibitor PF-573228 (Fig. 4A). Blockade of the FAK signaling pathway using PF-573228 increased E-cadherin expression and decreased Slug and vimentin expression (Fig. 4A). In contrast, PLST downregulation suppressed FAK and AKT phosphorylation, and treatment with PF-573228 amplified this effect (Fig. 4B). Furthermore, PLST downregulation and PF-573228 treatment increased E-cadherin expression and decreased Slug and vimentin expression (Fig. 4B). These results indicate that PLST regulates Slug expression through the FAK/AKT signaling pathway. In conclusion, we demonstrated that PLST induces EMT through Slug via phosphorylation of FAK and AKT in H460 and H1299 human lung cancer cells (Fig. 4C).

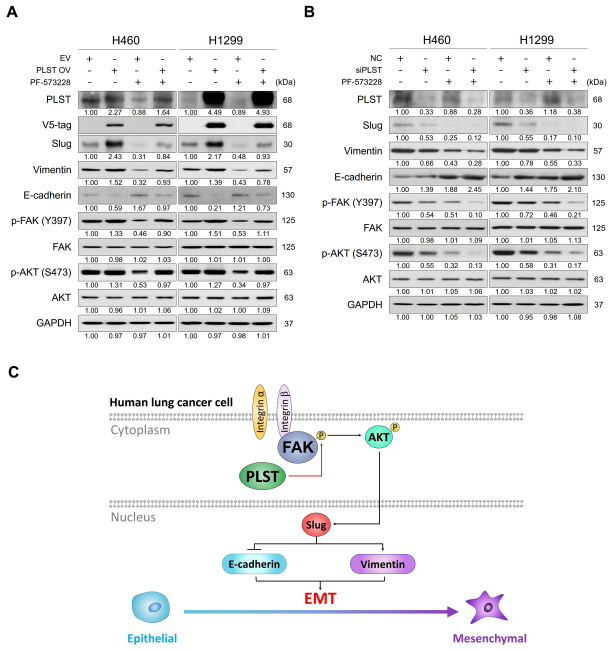

Fig. 4. The activation of FAK/AKT signaling pathway by PLST in H460 and H1299 cells. (A) Western blotting analysis was performed to determine the association between PLST-induced EMT and FAK/AKT signaling pathway. H460 and H1299 cells were transfected with EV or PLST OV for 24 h, and treated with nothing or 10 μM PF-573228, as an inhibitor of FAK, for 24 h. (B) Western blotting analysis was performed to confirm that FAK is involved in PLST-induced EMT signaling pathway. H460 and H1299 cells were transfected with NC or siPLST for 48 h, and treated with nothing or 10 μM PF-573228 for 24 h. These results are the average of three independent experiments. (C) A schematic model for the induction of EMT process by PLST in H460 and H1299 cells.

DISCUSSION

The plastin protein family consists of actin-bundling proteins that are conserved and expressed in diverse organisms, including yeast, plants, and mammalian cells (14). Plastin proteins participate in cytoskeletal modulation by controlling cell structure, arrangement, and polarity (15, 23). The plastin family comprises three isoforms: I-plastin (PLS1), L-plastin (LCP1 or PLS2), and T-plastin (PLST) (24). PLST is expressed in almost all mammalian cells in solid tissues (14). In previous studies, PLST was found to be overexpressed in the CTCs of breast and prostate cancers (16, 17). This suggests that PLST can be used as a biomarker for CTCs. Additionally, PLST is highly expressed in pancreatic cancer, where it activates the phosphoinositide 3-kinase (PI3K)/AKT signaling pathway and promotes cancer progression (25). Moreover, PLST overexpression in gastric and colorectal cancers induces EMT and is correlated with poor prognosis (18, 19). Based on Kaplan-Meier survival analysis from the Human Protein Atlas database, high expression of PLST is associated with poor prognosis in lung cancer patients. Despite research on the correlation between PLST and malignancy in some solid tumors, the role of PLST in human lung cancer remains unclear. Our study, which investigated the function of PLST in EMT of human lung cancer cells, suggests that PLST plays an important role in metastasis through Slug-mediated FAK/AKT signaling and is a potent therapeutic target protein in human lung cancer cells.

During EMT, cancer cells undergo morphological transformations accompanied by alterations in their molecular expression patterns. During this process, cells lose their epithelial features and acquire mesenchymal phenotypes, including changes in cell morphology, migratory behavior, and invasive properties (6, 11-13). As a result, the prominent epithelial marker E-cadherin decreases, whereas various factors such as Slug, Snail, and Twist, which are mesenchymal markers, increase (26). In particular, Slug is a key transcription factor capable of binding to the promoters of oncogenic genes, thereby enhancing the protein expression of C-C motif chemokine ligand 5, C-X-C motif chemokine ligand 12, and C-X-C motif chemokine receptor 4. These mechanisms contribute to the progression and malignancy of breast, prostate, and pancreatic cancer (27, 28). Moreover, reported clinical analysis indicates that high expression of Slug is associated with worse survival in lung cancer patients (29). Here, we identified that PLST regulates the expression of the oncogenic protein Slug, suggesting that elucidating the upstream regulators of Slug could provide a background for exploring tumor therapeutic mechanisms through

Slug suppression in lung cancer.

In this study, we demonstrated that PLST overexpression enhanced the mesenchymal phenotype as well as cell migration and invasion abilities, promoting EMT in H460 and H1299 human lung cancer cells (Fig. 1). Conversely, PLST downregulation attenuated these effects (Fig. 2). These results suggest that PLST acts as a cytoskeletal regulator and plays a role in the morphology and motility of lung cancer cells. Furthermore, Slug expression was significantly regulated by the levels of PLST expression (Fig. 3). PLST overexpression induced mesenchymal expression patterns, whereas PLST knockdown suppressed these expression patterns. Our data indicated that PLST triggered mesenchymal phenotypes through Slug-mediated EMT in H460 and H1299 cells.

FAK, a cytoplasmic protein tyrosine kinase, is localized in focal adhesions near the cytoplasmic membrane. FAK regulates cell adhesion, angiogenesis, proliferation, survival, and motility of various types of cells (30, 31). Additionally, it participates in the progression of tumors to malignant phenotypes in many cancers by activating the AKT signaling pathway (32, 33). The phosphorylation levels of FAK and AKT have been identified as associated with cancer development and poor prognosis in NSCLC patients (34, 35). Therefore, we focused on the FAK/AKT signaling pathway because of the association between LCP1, an isoform of PLST, FAK, and AKT, as well as their functional similarities. Overexpression of PLST stabilizes F-actin bundles, increasing their quantity and altering cell structure (36). As F-actin bundles increase within the cell, interactions with integrin are enhanced (37). This enhanced interaction with integrin induces FAK autophosphorylation, which then triggers the phosphorylation of AKT (32, 33, 38). Taken together, overexpression of PLST induces an increase in F-actin bundle formation, which may enhance interactions with integrin and subsequently induces the activation of FAK and AKT. These processes play a crucial role in regulating cell structure and motility. Our data showed that PLST expression levels regulated the phosphorylation of the FAK/AKT axis, and PLST knockdown or inhibition of FAK signaling effectively suppressed mesenchymal molecular phenotypes (Fig. 4). These results suggest that PLST accelerated EMT by activating the FAK/AKT axis in H460 and H1299 cells.

In conclusion, we demonstrated that Slug expression and EMT of human lung cancer cells may be controlled via the FAK/AKT signaling pathway, depending on PLST expression. Our study provides evidence that PLST is a potential diagnostic marker for the progression and therapy of lung cancer.

MATERIALS AND METHODS

Materials and methods are available in the supplementary information.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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