Original Article

PRDM14 Promotes the Migration of Human Non-small Cell Lung Cancer Through Extracellular Matrix Degradation *in vitro*

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Abstract

Background: As a novel molecular markerof non-small cell lung cancer (NSCLC), PRDI-BF1 and RIZ homology domain containing protein 14 (PRDM14) is over-expressed in NSCLC tumor tissues. Extracellular matrix degradation mediated by the balance between matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) is one of the most important mechanism in lung cancer metastasis. This study aimed to determine if PRDM14 promoted the migration of NSCLC cells through extracellular matrix degradation mediated by change of MMP/TIMP expression.

Methods: The expression of PRDM14 was down-regulated in human cell line A 549 after transfection with lentiviral vector-mediated short-hairpin ribonucleic acids (shRNAs) which targeted the PRDM14 promoter. Cellular migration of shRNA-infected cells was detected by a scratch wound healing assay and transwell cell migration assay. Expression levels of MMP1, MMP2, TIMP1, and TIMP2 were measured by quantitative real-time polymerase chain reaction (RT-PCR).

Results: Migration of PRDM14-shRNA-infected cells was significantly inhibited relative to control cells as measured by the scratch wound healing ($P < 0.05$) and transwell cell migration assays ($P < 0.01$). The expression of MMP1 in A549 cells infected by PRDM14-shRNA was down-regulated significantly ($P < 0.01$), whereas the expression of TIMP1 and TIMP2 was up-regulated significantly ($P < 0.01$).

Conclusions: PRDM14 accelerates A549 cells migration *in vitro* through extracellular matrix degradation. PRDM14 is considered as a potential therapeutic target in metastatic NSCLC.

Key words: Extracellular Matrix; Matrix Metalloproteinases; Neoplasm Metastasis; Non-small Cell Lung Cancer; Prdm14

Introduction

Non-small cell lung cancer (NSCLC) accounts for 80%–85% of all lung cancer cases.[1] Approximately, 25% have regional metastasis and 55% have distant metastasis were observed in patients initially diagnosed with NSCLC.[2] Despite therapeutic treatment with molecular-targeted drugs, such as target mutant erlotinib, gefitinib, and afatinib (EGFR) and mutant anaplastic lymphoma kinase (ALK) (crizotinib and ceritinib), the overall prognosis of these patients is not improved and is instead associated with drug resistance.[3] As a result, new agents targeting novel molecular targets are required for the therapeutic treatment of NSCLC metastasis.

The positive regulatory domain I-binding factor 1 and retinoblastoma protein-interacting zinc finger gene homology domain containing (PRDI-BF1 and RIZ homology domain containing, PRDM) family is a novel transcription regulator containing a N-terminal positive regulatory domain, followed by six deoxyribonucleic acid (DNA)-binding C2H2 zinc finger domains involved in human tumorigenesis.[4-11] Recently, PRDM14, a member of the PR domain-containing family of transcription factors, was found over-expressed in NSCLC tissues and is marginally expressed in paracancerous tissues, detected by immunohistochemistry and Western blot, where the expression level was positively correlated with differentiation.[12] Interestedly, PRDM14 is mapped to chromosome region 8q13.3, which is a domain involved in tumorigenesis and cancer development.[13-24] We were supposed that PRDM14 may play an important role in the development of NSCLC. Despite this, the function of PRDM14 in NSCLC development, especially metastasis, is largely unknown.

Matrix metalloproteinases (MMPs), such as MMP1 and MMP2, are extracellular matrix (ECM)-degrading

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enzymes that function in the extracellular environment of cells to degrade both matrix and non-matrix proteins,[25,26] and their activities are regulated by tissue inhibitor of metalloproteinases (TIMPs).[27] Thus, both MMPs and TIMPs are involved in lung cancer metastasis.[25]

The aim of this study was to determine the role and mechanism of PRDM14 in NSCLC metastasis by down-regulating PRDM14 expression in the human NSCLC cell line A549 using lentiviral vector-mediated small hairpin ribonucleic acids (shRNAs). We subsequently measured cell migration and MMP/TIMPs messenger RNA (mRNA) expression of PRDM14-shRNA infected cells to determine if PRDM14 promotes cell migration via extracellular matrix degradation mediated by change of MMP/TIMP expression.

Methods

Lentiviral vector-mediated shRNAs interference

Two shRNA primers which targeted PRDM14 were designed (A: CGTCCTATGGACACTACAGAA, B: GTGGGAAATGTTTCTCTCAAT). shRNA primer annealing (100 μl): Primer F (10 μm) 10 μl, Primer R (10 μm), 10 μl, 10 × Annealing buffer 10 μl, ddH_2O70 μl. Connect to viral vector: Connect system (10 μl): shRNA 4 μl, vector 2 μl, ddH_2O 2 μl, 10 × T4 buffer 1 μl, Roche T4 ligase 1 μl, 24°C × 2 hours. Transfer: 5 μl viral vector production was transfer into *Escherichia coli* strain Genehogs (Invitrogen, Dorset, UK).

A549 cells with PRDM14 shRNA knockdown were generated using a lentiviral-mediated delivery system as described previously.[28] Briefly, double-stranded oligos were inserted into the BamHI/EcoRI site of pUCTP vector, which contains a red fluorescent protein (tdTomato) marker for cell tracking. A549 cells infected only by pUCTP vector without containing PRDM14 shRNA were set as control group (shControl). The day before transfection, 293T cells in logarithmic phase growth planted into 96-well plates at 1 × 10^6 cells/well. Lentiviral vectors were transfected into 293T cells together with three packaging plasmids: pGag-pol, pVSVG, and pRev. The transfection reagent protocol is followed. 293T cells were cultured for 24 hours, 0.1–0.5 μg/well of deoxyribonucleic acid (DNA) was combined with 0.25 μl of transfection reagent. The virus supernatant was diluted by serum-free Dulbecco's modified Eagle's medium (DMEM) medium.

Mixed shRNA lentivirus plasmids

293T cells were transfected with lentiviral plasmid/helper plasmid. Virus supernatant was collected after 48 hours and 72 hours, and then cryopreservated at -80℃. A549 cells (2500 cells per well) were seeded into 96 well plates. The lentivirus particles, produced from the transfected 293T cells, were used to infect A549 cells in the presence of 8 μg/ml polybrene. The shControl group was prepared by transfecting A549 cells with an empty vector. Ninety-six hours after infection, the knockdown efficiency was validated by quantitative polymerase chain reaction (qPCR).

Quantitative real-time PCR

PRDM14 knockdown efficiency was validated by qPCR

qPCR primers of PRDM14 (F: TGGAGACAGACCA TACCAGTGT, R: TGATGTGTGTGCGGAGTATG) and β-Actin (F: GCATCCCCCA AAGTTCACAA, R: GGACTTCCTGTAACAACGCATCT) were designed with Primer Premier 6.0 and OLIGO Primer Analysis Software Version 7.0. Total RNA was extracted from cell lines using TRIzol reagent (Invitrogen, Life Technologies GmbH, Darmstadt, Germany, Cat. 15596-018). Complementary DNA (cDNA) was synthesized from 2 μg of RNA using PrimeScript™ real-time PCR (RT-PCR) Kit (TaKaRa, Cat. No.RR014A/B). qPCR was carried out using CFX Connect Real-Time PCR Detection System (BiaRad, 185-5200, USA). All samples were analyzed in triplicate. Gene expression was calculated relative to expression of housekeeping gene β-actin and adjusted relative to expression in shControl-infected cells.

MMP/TIMP mRNA expression was detected by qPCR

qPCR primers of MMP1 (F: TCGATGCTGCTCTTTCTGAG, R: GATAACCTGGATCCATAGATCGTT), MMP2 (F: TGCTGGAGACAAATTCTGGA, R: GATGGCATTCCAGGCATC), TIMP1 (F: TTTGTGGCTCCCTGGAACAG, R: CATTCCTCACAGCCAACAGTGT), TIMP2 (F:GAAGGAGCCCCATCAATCCT,R:CTCCCATTTCTACA AGGCTCAGA) were also designed with Primer Premier 6.0 and OLIGO Primer Analysis Software Version 7.0. The qPCR protocol described above was followed.

Scratch wound healing assay

A549 cells were grown in DMEM supplemented with 10% fetal bovine serum (FBS). Cells were seeded into 24-well tissue culture plate at a density of 1 × 10^5 cells/ml. After 24 hours of growth, the monolayer was scratched with a new 1 ml pipette tip across the center of the well. The extent of cell migration was photographed after another 24 hours (Axio Vert A1 FL, Carl Zeiss, Germany) and measured using image analyzing software (Axio CSM 700, Carl Zeiss, Germany). Each experiment was performed in triplicate.

Transwell cell migration assays

Cell migration was performed in Boyden chambers using 8-μm-pore-size polyethylene terephthalate membranes with a Falcon cell-culture insert (BD Biosciences, Bedford, MA). Moreover, 2.5 × 10^4 cells were pre-infected by PRDM14 shRNA lentivirus in 100 μl serum-free medium were added to the upper chamber, and 500 μl medium with 10% FBS were added to the lower chamber. The filter was inserted into the lower chamber and incubated for 24 hours at 37°C. Cells on the top side of the filter were removed by scrubbing twice with cotton tipped swab moistened with PBS. Cells on the underside of the insert filter were fixed and stained for 1

hour with Crystal violet solution (Sigma, HT90132, USA) in 2% ethanol. Images were taken of five random fields of view and the cells were counted to calculate the average number of cells that migrated across the filters after 24 hours as described previously.[7]

Statistical analysis

All data was presented as mean ± standard error and analyzed by *t*-test using Statistical Package for the Social Sciences (SPSS) 16.0 statistical software (SPSS Inc., USA). $P < 0.05$ was considered statistically significant. The correlation between indexes was also analyzed.

Results

PRDM14 knockdown efficiency validation

We knocked down PRDM14 expression in human NSCLC cell line A549 using lentiviral vector-mediated shRNAs. The transfection efficiency of PRDM14-knockdown was validated by colony PCR, enzyme digestion, and qPCR; the results showed that mRNA expression of PRDM14 in A549 was down-regulated significantly relative to the shControl group ($P < 0.05$) [Figure 1].

PRDM14 promotes A549 cells migration *in vitro*

The result of cell scratch wound healing assay showed the migration distance of A549 cells infected by shRNAs (194.66 ± 34.74 μm) was significantly shorter than the shControl group (270.58 ± 30.20 μm) ($P = 0.0353$; < 0.05) [Figure 2]. In the transwell assay, the number of PRDM14-shRNA infected cells (290.50 ± 99.21 cells/well) that migrated through the membrane was significantly less than the shControl group (562.70 ± 174.28 cells/well) ($P = 0.032$) [Figure 3].

MMP/TIMP expression in A549 cells infected by PRDM14-shRNA

The result of qPCR showed that the mRNA expression of MMP1 was down-regulated while TIMP1 and TIMP2 were up-regulated significantly in PRDM14-shRNA group. The expression of MMP2 was comparable to the shControl group [Figure 4].

Discussion

As a transcription factor, PRDM14 plays a significant role in the maintenance of self-renewal of human or mouse emryonic stem cell identity.[29-31] Stem cells and cancer

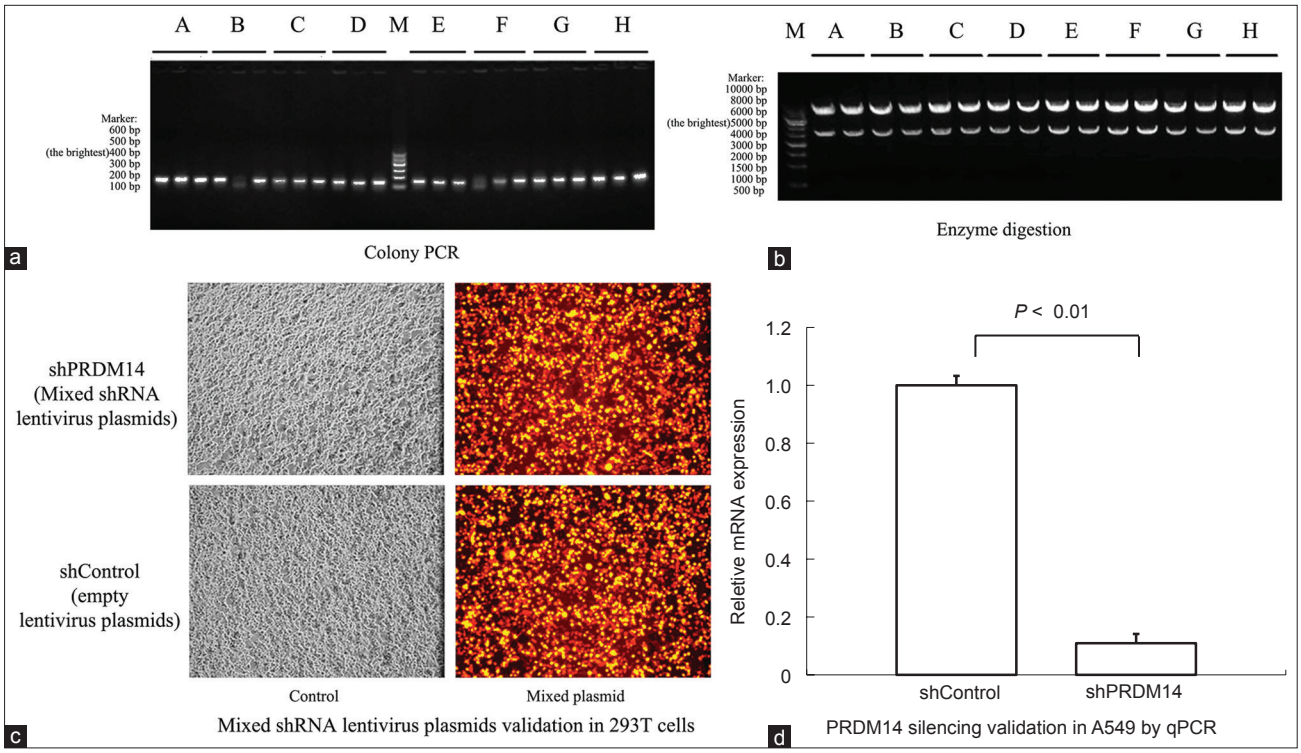

Figure 1: (a) Colony polymerase chain reaction (PCR) was used after a transformation to screen colonies for PRDI-BF1 and RIZ homology domain containing protein 14 (PRDM14) short-hairpin ribonucleic acid (shRNA) plasmid. The primers used generate a PCR product of 170 bp, positive clones displayed are specific amplified bands of approximately 170 bp fragments. Marker: 600 bp/500 bp/400 bp (the brightest)/300 bp/200 bp/100 bp (from top to bottom) which give rise to an amplification product containing the PRDM14 deoxyribonucleic acid (DNA) sequence. (b) Each fragment is selected by two positive clones and digested with KPNI restriction enzyme to generate a 2.95 Kb and 7.5 Kb fragment. Marker: 10000 bp/8000 bp/6000 bp/5000 bp/(the brightest)/4000 bp/3000 bp/2000 bp/1500 bp/1000 bp/500 bp (from top to bottom). (c) Serum-free Dulbecco's modified Eagle's medium (DMEM) medium was used to dilute the viral supernatant. shRNA lentiviral plasmid mixture were used for viral packaging, respectively. Each gene corresponded to two hybrid viruses. 293T cells were transfected with lentiviral plasmid/helper plasmid. (d) PRDM14 silencing validation in A549 by qPCR: Messenger RNA (mRNA) expression of PRDM14 in A549 cells of shPRDM14 group was significantly down-regulated relative to the shControl group.

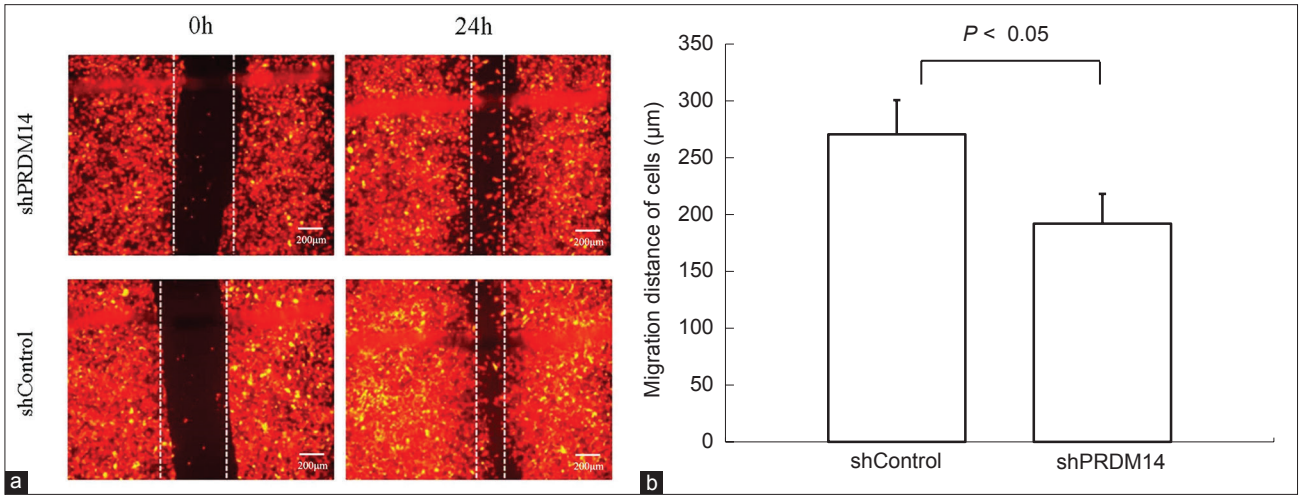

Figure 2: (a) Cells migration in cell scratch wound healing assay: A549 cells were seeded into 24-well tissue culture plate at a density of 1×10^5 cells/ml, the monolayer was scratched with a new 1 ml pipette tip across the center of the well. The extent of cell migration was photographed after another 24 hours and measured using image analyzing software. (b) Comparison bar graph: The result showed the migration distance of A549 cells of shPRDM14 group (192.02 ±26.17 μm) was significantly shorter than the shControl group (270.58 ± 30.20 μm) ($P = 0.035$).

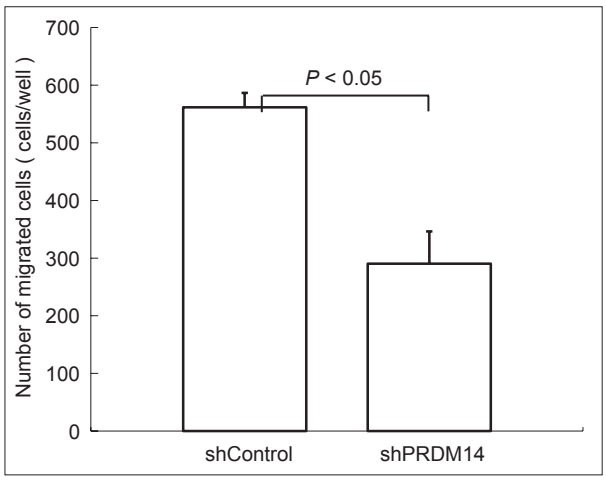

Figure 3: Cells migration in transwell assay: 2.5×10^4 A549 cells were pre-infected by PRDM14-shRNA in 100 μl serum-free medium were added to the upper chamber of Falcon cell-culture insert (BD Biosciences, Bedford, MA), and 500 μl medium with 10% fetal bovine serum (FBS) were added to the lower chamber. The filter was inserted into the lower chamber and incubated for 24 hours at 37°C. In the transwell assay, the number of A549 cells of shPRDM14 group (290.50 ± 25.00 cells/well) that migrated through the membrane was significantly less than the shControl group (561.55 ±55.80 cells/well) ($P = 0.032$).

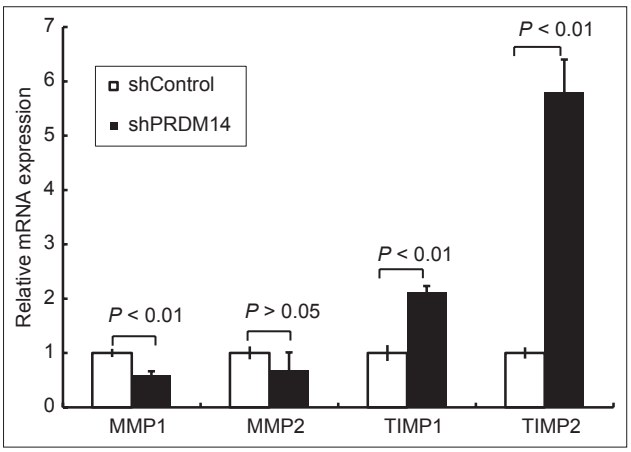

Figure 4: As compared with shControl group ($2^{-\Delta\Delta ct} = 1.000 \pm 0.010$), the expression of matrix metalloproteinase 1 (MMP1) was down-regulated significantly ($2^{-\Delta\Delta ct} = 0.597 \pm 0.067$; $P = 0.000$, < 0.01), while tissue inhibitor of metalloproteinase 1 (TIMP1) ($2^{-\Delta\Delta ct} = 2.121 \pm 0.113$; $P = 0.0002$) and TIMP2 ($2^{-\Delta\Delta ct} = 5.810 \pm 0.591$; $P < 0.0001$) was significantly up-regulated in shPRDM14 group. The expression of MMP2 was comparable to the shControl group ($P > 0.05$).

cells are reported to display some similar properties in self-renewal and blocked differentiation.[12] As a proto-oncogene, PRDM14 is also involved in lymphoblastic lymphoma formation.[32] and is over-expressed in human T-cell acute and hyperdiploid precursor B-cell acute lymphoblastic lymphoma, which is involved in leukemia initiation.[33] PRDM14 is frequently over-expressed in breast cancers (with minimal expression in normal tissue), enhances breast cancer cells growth and reduces the susceptibility of cancer cells to chemotherapeutic drugs.[34] As a novel molecular marker of NSCLC, PRDM14 protein is over-expressed in NSCLC tumor tissues.[12] However, the functional role of PRDM14 in the progression of NSCLC is largely unknown. In this study, the migratory capacity of PRDM14-shRNA infected A549 cells were detected by a scratch wound healing and transwell cell migration assay, we found PRDM14 significantly promoted A549 cells migration in both migration assays [Figures 3 and 4], and PRDM14 may be a novel target for anti-lung cancer with metastasis.

Extracellular matrix degradation is mediated positively by the rate of in MMPs/TIMPs expression, which is a key mechanism inlung cancer metastasis.[25] To determine the relationship between migration of NSCLC by PRDM14 and MMPs/TIMPs expression, we measured the mRNA expression levels of MMP1-2 and TIMP1-2 in PRDM14-shRNA-infected A549 cells. In our study, we found that expression of

MMP1 in A549 cells infected by PRDM14-shRNA was down-regulated significantly, while the expression of TIMP1 and TIMP2 was up-regulated significantly [Figure 4]. Our study suggests that PRDM14 promotes A549 cells metastasis by extracellularmatrix degradation through the up-regulation of MMP1 and down-regulation TIMP1 and TIMP2. The other cancer-associated roles and mechanism of PRDM14 should be further explored in additional studies.

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