Pathology - Research and Practice 215 (2019) 152603

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

miR-182 contributes to cell adhesion-mediated drug resistance in multiple myeloma via targeting PDCD4

Yaxun Wu[a,1], Xinghua Zhu[a,1], Rong Shen[a], Jieyu Huang[a], Xiaohong Xu[b,*], Song He[a,*]

[a] Department of Pathology, Affiliated Tumor Hospital of Nantong University, Nantong, 226361, Jiangsu, China
[b] Department of Oncology, Affiliated Tumor Hospital of Nantong University, Nantong, 226361, Jiangsu, China

ARTICLE INFO

Keywords:
Multiple myeloma
Cell adhesion-mediated drug resistance
miR-182
Programmed cell death 4

ABSTRACT

miR-182 is a well-described oncogenic miRNA playing a crucial role in the development of many malignancies. However, the role of miR-182 in multiple myeloma (MM) remains unclear. Here, we demonstrate that adhesion of H929 and MM.1S cells to fibronectin could induce miR-182 expression and decrease PDCD4 expression. Furthermore, miR-182 was found to negatively regulate PDCD4 expression in H929 and MM.1S cells. In addition, PDCD4 down-regulation was required for cell adhesion-mediated drug resistance (CAM-DR). Intriguingly, miR-182 up-regulation could promote CAM-DR in H929 and MM.1S cells. Moreover, miR-182 up-regulation and PDCD4 down-regulation enhanced AKT phosphorylation at Ser473 in both H929 and MM.1S cells. Our data suggest that cell adhesion-mediated miR-182 up-regulation and PDCD4 down-regulation may confer drug resistance via enhancing AKT phosphorylation at Ser473.

1. Introduction

Multiple myeloma (MM) is a clonal plasma cell disorder predominantly affecting the elderly [1]. Significant progress in MM has been achieved over the past decade with novel therapeutics. However, these therapeutics may gradually lose efficacy in relapsed, refractory MM [2]. Mounting evidence now suggests that the direct adhesive interactions between the MM cells and the surrounding microenvironment transduce into the former anti-apoptotic or pro-survival signals leading to drug resistance. This type of drug resistance, termed 'cell adhesion-mediated drug resistance' (CAM-DR), is thought to be one of the most important mechanisms responsible for the escape of MM cells from the therapeutic effects [3,4]. Thus, elucidation of the molecular mechanisms underlying CAM-DR may help identify novel therapeutic approaches to this problem.

MicroRNAs (miRNAs) are a large class of 18- to 24- nucleotide noncoding RNAs that can post-transcriptionally regulate target-gene expression, either by inhibiting translation or accelerating RNA degradation [5]. Recent studies have demonstrated that some miRNAs can modulate the drug response of MM cells through the regulation of apoptotic, anti-apoptotic or proliferative signaling pathways [6]. Wang et al. [7] reported that adhesion of MM cells to bone marrow stromal cells could induce miR-21 expression, thereby reducing apoptosis in response to anti-myeloma drugs. The above indicates that adhesion of MM cells to tumor microenvironment can alter miRNA expression leading to drug resistance. miR-182 is a well-described oncogenic miRNA playing a crucial role in the development of many malignancies including glioma, lung, breast, prostate, liver and colorectal cancers [8]. In a recent study, Zhang et al. [9] demonstrated that inhibition of miR-182 could decrease cell proliferation and reverse cisplatin resistance via targeting BCL2L12 and BCL2 expression in acute myeloid leukemia. Chen et al. [10] reported that miR-182 could enhance radioresistance by regulating FOXO3 in non-small cell lung cancer. However, the role of miR-182 in MM remains unclear and needs further investigation.

Bioinformatic analysis reveals that the 3′ untranslated region (UTR) of the human programmed cell death 4 (PDCD4) gene contains miR-182 target sites. PDCD4 is frequently down-regulated in many cancers and acts as a tumor suppressor. Ning et al. [11] reported that miR-182 could modulate chemosensitivity of non-small cell lung cancer cells to cisplatin via targeting PDCD4. miR-182 has also been found to enhance chemoresistance of ovarian cancer cells to cisplatin and taxol through negatively regulating PDCD4 [12]. In this study, we investigated the effect of miR-182 on CAM-DR, and determined whether miR-182 could potentially contribute to CAM-DR via targeting PDCD4 in MM.

* Corresponding authors.
E-mail addresses: xuxiaohongnantong@126.com (X. Xu), ntzlyyhesong515@ntu.edu.cn (S. He).
[1] Yaxun Wu and Xinghua Zhu have contributed equally to this work.

https://doi.org/10.1016/j.prp.2019.152603
Received 10 June 2019; Received in revised form 1 August 2019; Accepted 16 August 2019

2. Materials and methods

2.1. Cell lines and cell cultures

The human MM cell lines NCI-H929 (H929) and MM.1S were obtained from Cobioer Biosciences Co., Ltd. (Nanjing, China), and were maintained in RPMI-1640 medium (Gibco-BRL, Grand Island, NY, USA) containing 10% fetal bovine serum (Gibco-BRL). All cell cultures were incubated in 5% CO_2 at 37 °C.

2.2. Cell adhesion

Ninety-six-well plates (Corning Incorporated, Corning, NY, USA) were coated with 50 μL (40 μg/mL) fibronectin (FN, Sigma-Aldrich, St. Louis, MO, USA) and allowed to slowly evaporate overnight. MM cells were washed once and then resuspended in serum-free medium. After resuspension, 5×10^4 cells were added to each well. After 24 h of adhesion, unattached cells were removed by washing three times with serum-free medium.

2.3. Lentivirus infection

The lentiviral vectors over-expressing miR-182 (Lv-miR-182), PDCD4 (Lv-PDCD4) or down-expressing miR-182 (Lv-sh-miR-182), PDCD4 (Lv-sh-PDCD4) were constructed by GeneChem (Shanghai, China). Lentivirus infection was carried out according to the manufacturer's instructions (GeneChem).

2.4. Western blot

Western blot was carried out by the methods described earlier [13]. Antibodies used in this study included: anti-PDCD4 antibody (1:500, Santa Cruz Biotechnology, Santa Cruz, CA, USA), anti-β-actin antibody (1:1000, Santa Cruz Biotechnology), anti-AKT antibody (1:1000, Cell Signaling Technology, Beverly, MA, USA), anti-$pAKT^{Ser473}$ antibody (1:1000, Cell Signaling Technology).

2.5. Quantitative RT-PCR

Total RNAs isolated from cells using Trizol Reagent (Invitrogen, Carlsbad, CA, USA) were reverse-transcribed into cDNA according to the manufacturer's instructions. Quantitative real-time RT-PCR was performed using SYBR Green PCR reagents (TaKaRa, Dalian, China). Amplification and detection were carried out using ABI 7900 H T system (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's recommended protocol. miR-182 and *PDCD4* mRNA levels were normalized with U6 small RNA and *GAPDH* mRNA expression, respectively. Relative levels were calculated by using the comparative cycle threshold (CT) method. The qPCR primers for miR-182, U6, PDCD4 and GAPDH were purchased from GeneChem. The sequences of the primers were as follows: miR-182 (forward: 5′-ACACTCCAGCTGGGTTTGGCAATGGTAGAACT-3′; reverse: 5′-TGGTGTCGTGGAGTCG-3′), U6 (forward: 5′-CTCGCTTCGGCAGCACATATACT-3′; reverse: 5′-ACGCTTCACGAATTTGCGTGTC-3′), *PDCD4* (forward: 5′-TTGGCAGTATCCTTAGCATTG-3′; reverse: 5′-CAGAAGCACGGTAGCCTTATC-3′), *GAPDH* (forward: 5′-TGACTTCAACAGCGACACCCA-3′; reverse: 5′-CACCCTGTTGCTGTAGCCAAA-3′).

2.6. Luciferase reporter assay

Wild type (WT) or mutant (Mut) PDCD4 3′UTRs were amplified by PCR from cDNAs and cloned into the luciferase reporter vector GV272 (Genechem). 293 T cells were seeded in 24-well plates and co-transfected with miR-182 mimic (50 nM) or Ctrl-mimic (Ribobio, Guangzhou, China), 0.1 μg of 3′UTR luciferase construct and 0.02 μg of TK-Renilla plasmid using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. Forty-eight hours after transfection, cells were harvested and luciferase activity was measured using the Dual-luciferase® Reporter Assay System (Promega, Madison, WI, USA) according to the manufacturer's instructions. Firefly luciferase activity was normalized by Renilla luciferase activity.

2.7. Trypan blue exclusion assay

Trypan blue exclusion assay was performed following the procedure described previously [13]. The percentage of dead cells was calculated with the following formula: number of dead cells / (number of living cells + number of dead cells) × 100%.

2.8. Statistical analysis

Statistical analyses were performed with GraphPad Prism (GraphPad Software Inc., San Diego, USA). Student's *t*-test was used for statistical analysis. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Adhesion of MM cells to FN induces miR-182 expression and decreases PDCD4 expression

First, we examined whether adhesion of MM cells to FN could lead to changes in miR-182 and PDCD4 expression levels. Our qRT-PCR data showed that adhesion of H929 and MM.1S cells to FN (FN) significantly upregulated the level of miR-182, when compared to their suspension (Sus) counterparts (Fig. 1A). In contrast, Western blot analysis demonstrated that PDCD4 protein expression was obviously decreased upon cell adhesion to FN in H929 and MM.1S cells (Fig. 1B).

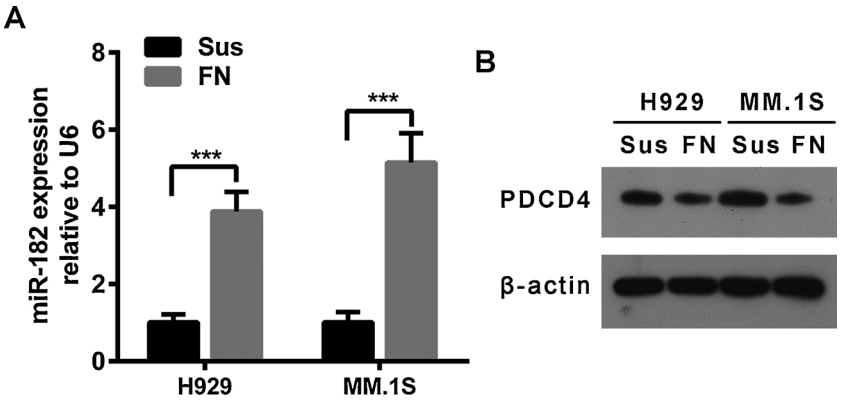

Fig. 1. *Adhesion of MM cells to FN induces miR-182 expression and decreases PDCD4 expression.* (A) H929 and MM.1S cells were cultured in uncoated (suspension, Sus) or FN-coated (FN) plates for 24 h. The cells were then harvested and analyzed for miR-182 expression by qRT-PCR assays. U6 RNA served as an internal control. ***, $P < 0.001$, determined by Student's *t*-test (B) H929 and MM.1S cells were cultured in uncoated or FN-coated plates for 24 h. The cells were then collected and analyzed for PDCD4 expression by Western blot. β-actin served as a loading control.

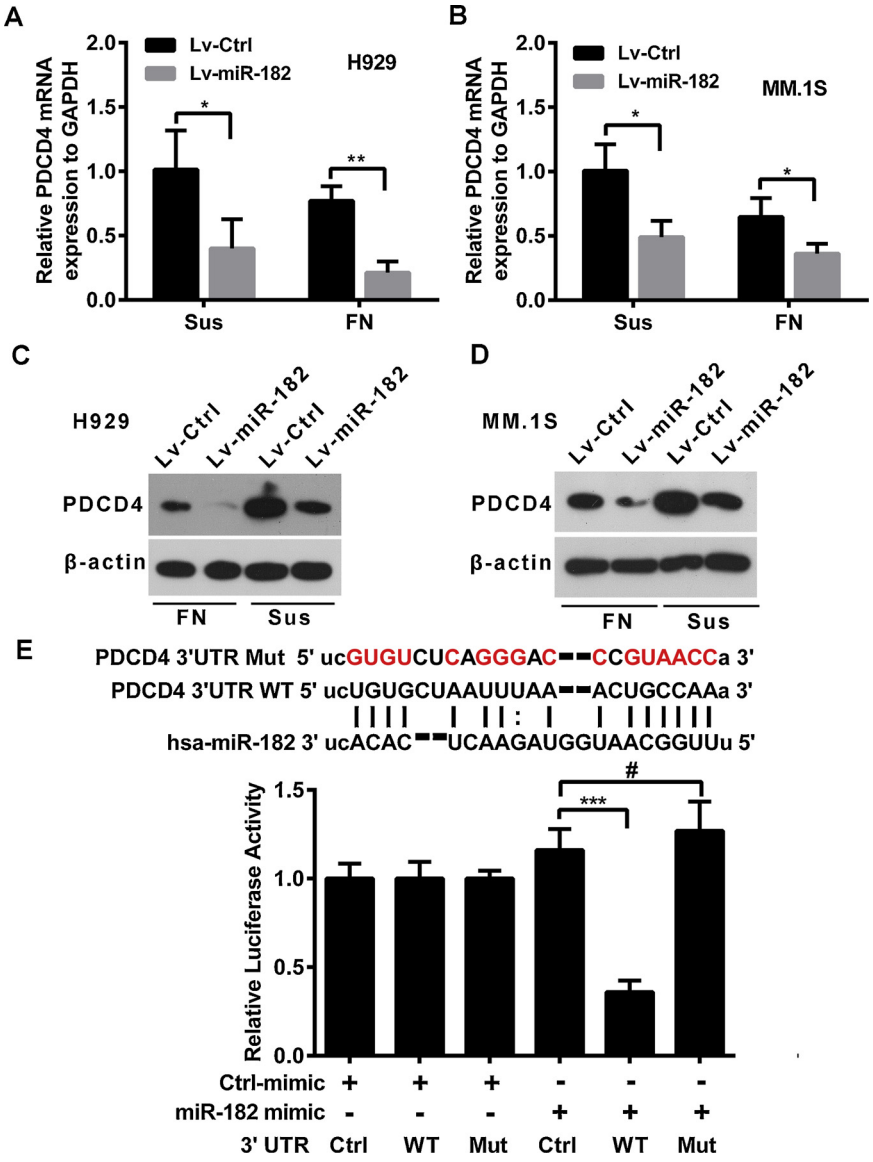

Fig. 2. *miR-182 negatively regulates PDCD4 expression in MM cells.* (A, B) H929 and MM.1S cells were infected with Lv-miR-182 or its negative control (Lv-Ctrl) for 72 h. Then, the cells were cultured in uncoated or FN-coated plates for 24 h, and *PDCD4* mRNA expression was analyzed by qRT-PCR assays. *GAPDH* served as an internal control. *, $P < 0.05$, **, $P < 0.01$, determined by Student's *t*-test (C, D) H929 and MM.1S cells were infected with Lv-miR-182 or Lv-Ctrl for 72 h. Then, the cells were cultured in uncoated or FN-coated plates for 24 h, and PDCD4 protein expression was analyzed by Western blot. β-actin served as a loading control. (E) Control luciferase reporter (Ctrl), luciferase reporter with wild-type PDCD4 3′UTR (WT) or mutant PDCD4 3′UTR (Mut) was cotransfected into 293T cells with miR-182 mimic or Ctrl-mimic. Luciferase activity was determined by the dual luciferase assay. Firefly luciferase activity was normalized by Renilla luciferase activity. ***, $P < 0.001$, $^{\#}$, $P > 0.05$, determined by Student's *t*-test.

3.2. miR-182 negatively regulates PDCD4 expression in MM cells

Recently, miR-182 has been reported to directly and negatively regulate PDCD4 expression in several cancer cells [11,12]. We then asked whether miR-182 could also regulate PDCD4 expression in MM cells. H929 and MM.1S cells were infected with Lv-miR-182 or its negative control (Lv-Ctrl) for 72 h. Then, the cells were cultured in uncoated or FN-coated plates for 24 h, and were then harvested for qRT-PCR and Western blot analysis. Our results showed that ectopic expression of miR-182 markedly decreased *PDCD4* mRNA (Fig. 2A, B) and protein (Fig. 2C, D) expression in both suspension and FN-adherent H929 and MM.1S cells. To verify whether PDCD4 is indeed a direct target of miR-182, we mutated the predicted miR-182 binding site in the PDCD4 3′UTR and inserted the mutated sequence into the luciferase reporter vector GV272. As shown in Fig. 2E, ectopic expression of miR-182 significantly reduced the relative luciferase activity of the wild-type construct of PDCD4 3′UTR, whereas mutation of the putative miR-182 binding site abolished the suppressing effects of miR-182. Taken collectively, these data indicate that miR-182 could negatively regulate PDCD4 expression in MM cells.

3.3. PDCD4 down-regulation is required for CAM-DR in MM

We then determined whether PDCD down-regulation is required for CAM-DR in MM. To address this issue, we infected H929 and MM.1S cells with PDCD4-RNAi-lentivirus (Lv-sh-PDCD4) or its negative control (Lv-sh-Ctrl) for 72 h. Then the cells were treated with 1.0 μM doxorubicin (Doxo) or DMSO for 72 h in the presence or absence of FN adhesion. Trypan blue exclusion assay was then used to analyze Doxo-induced cell death. As shown in Fig. 3A and B, adhesion of H929 and MM.1S cells to FN protected the cells against Doxo-induced cell death. Importantly, silencing of PDCD4 conferred resistance to Doxo-induced cell death in both suspension and FN-adherent H929 and MM.1S cells. We further investigated the effects of overexpression of PDCD4 on CAM-DR. As anticipated, ectopic expression of PDCD4 enhanced Doxo-induced cell death, and partially abolished CAM-DR in both H929 and MM.1S cells (Fig. 3C, D). Taken together, the above data support the crucial role of PDCD4 in CAM-DR in MM.

3.4. miR-182 up-regulation promotes CAM-DR in MM

We next determined the effects of overexpression of miR-182 on CAM-DR. H929 and MM.1S cells were infected with Lv-miR-182 or Lv-Ctrl for 72 h. Then the cells were treated with 1.0 μM Doxo or DMSO for

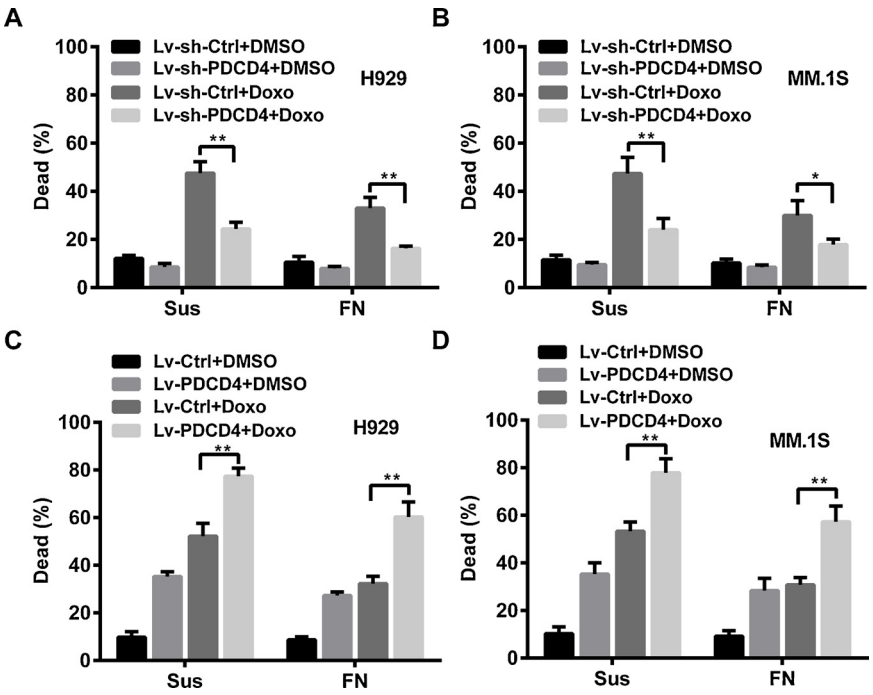

Fig. 3. *PDCD4 down-regulation is required for CAM-DR in MM.* (A, B) H929 and MM.1S cells were infected with Lv-sh-PDCD4 or Lv-sh-Ctrl for 72 h, then the cells were treated 1.0 μM doxorubicin (Doxo) or DMSO for 72 h in the presence or absence of FN adhesion. Doxo-induced cell death was analyzed by trypan blue exclusion assay. Data shown are the mean ± SEM of three independent experiments. *, $P < 0.05$, **, $P < 0.01$, determined by Student's *t*-test (C, D) H929 and MM.1S cells were infected with Lv-PDCD4 or Lv-Ctrl for 72 h, then the cells were treated 1.0 μM Doxo or DMSO for 72 h in the presence or absence of FN adhesion. Doxo-induced cell death was analyzed by trypan blue exclusion assay. Data shown are the mean ± SEM of three independent experiments. **, $P < 0.01$, determined by Student's *t*-test.

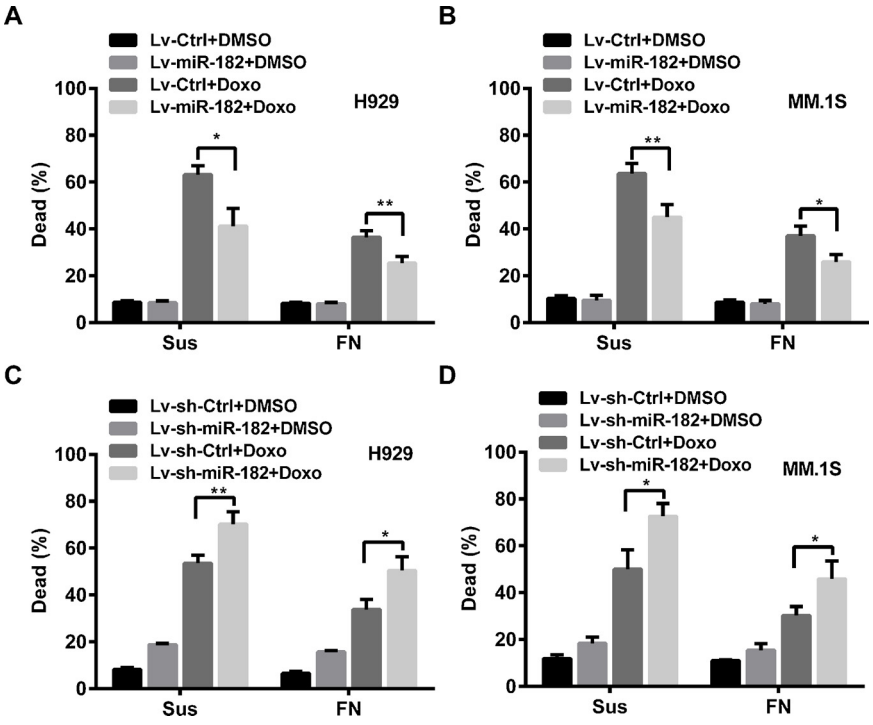

Fig. 4. *miR-182 up-regulation promotes CAM-DR in MM.* (A, B) H929 and MM.1S cells were infected with Lv-miR-182 or Lv-Ctrl for 72 h, then the cells were treated 1.0 μM Doxo or DMSO for 72 h in the presence or absence of FN adhesion. Doxo-induced cell death was analyzed by trypan blue exclusion assay. Data shown are the mean ± SEM of three independent experiments. *, $P < 0.05$, **, $P < 0.01$, determined by Student's *t*-test (C, D) H929 and MM.1S cells were infected with Lv-sh-miR-182 or Lv-sh-Ctrl for 72 h, then the cells were treated 1.0 μM Doxo or DMSO for 72 h in the presence or absence of FN adhesion. Doxo-induced cell death was analyzed by trypan blue exclusion assay. Data shown are the mean ± SEM of three independent experiments. *, $P < 0.05$, **, $P < 0.01$, determined by Student's *t*-test.

72 h in the presence or absence of FN adhesion. Trypan blue exclusion assay showed that overexpression of miR-182 suppressed Doxo-induced cell death in both suspension and FN-adherent H929 and MM.1S cells, suggesting that overexpression of miR-182 enhanced CAM-DR in MM (Fig. 4A, B). To further confirm the role of miR-182 in regulation of CAM-DR, we infected H929 and MM.1S cells with miR-182 inhibition lentivirus (Lv-sh-miR-182) or its negative control (Lv-sh-Ctrl) for 72 h. As depicted in Fig. 4C and D, ectopic inhibition of miR-182 increased Doxo-induced cell death, and also partially abolished CAM-DR in both H929 and MM.1S cells. These findings collectively suggest that cell adhesion-mediated increased miR-182 expression and decreased PDCD4 expression are required for CAM-DR.

3.5. miR-182 up-regulation and PDCD4 down-regulation enhances AKT phosphorylation at Ser473

Deregulated activity of the AKT has been implicated in mediating CAM-DR [14]. To determine whether miR-182 and PDCD4 are involved in CAM-DR through enhancing AKT activation, we next examined the effects of miR-182 up-regulation and PDCD4 down-regulation on pAKT expression. H929 and MM.1S cells were infected with Lv-miR-182 or Lv-Ctrl for 72 h. Then, the cells were harvested for Western blot analysis. As shown in Fig. 5A, ectopic expression of miR-182 enhanced AKT phosphorylation at Ser473 in both H929 and MM.1S cells. Similar results were observed after PDCD4 knockdown in both H929 and MM.1S

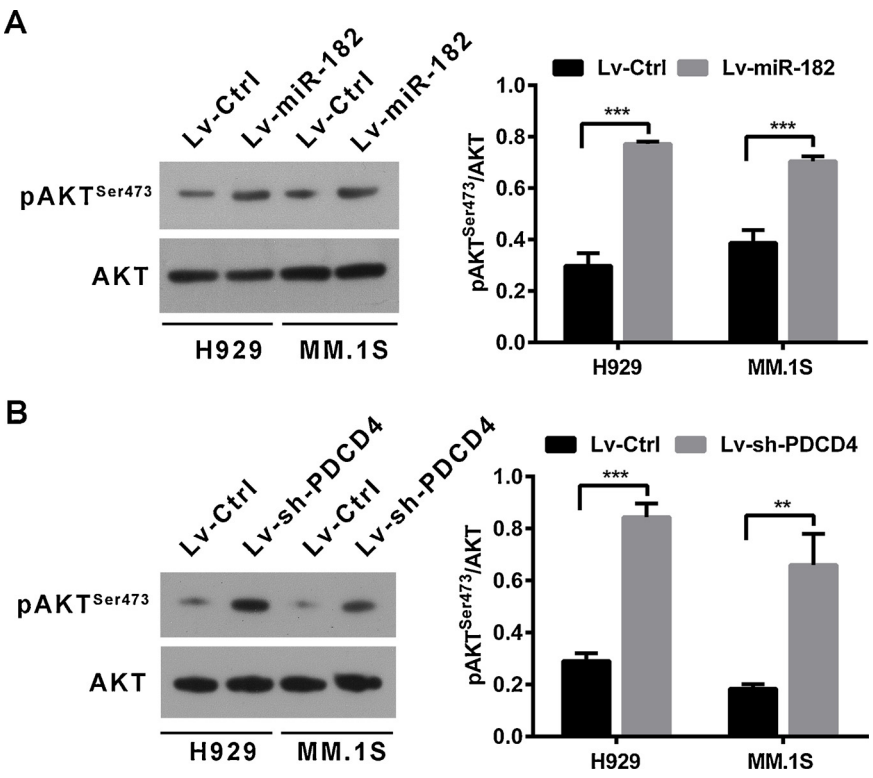

Fig. 5. *miR-182 up-regulation and PDCD4 down-regulation enhances AKT phosphorylation at Ser473.* (A) H929 and MM.1S cells were infected with Lv-miR-182 or Lv-Ctrl for 72 h. AKT and $pAKT^{S473}$ expression were analyzed by Western blot. The Western blot is shown at the left, and densitometry result is shown at the right. Data shown are the mean ± SEM of three independent experiments. ***, $P < 0.001$, determined by Student's *t*-test (B) H929 and MM.1S cells were infected with Lv-sh-PDCD4 or Lv-sh-Ctrl for 72 h. AKT and $pAKT^{S473}$ expression were analyzed by Western blot. The Western blot is shown at the left, and densitometry result is shown at the right. Data shown are the mean ± SEM of three independent experiments. **, $P < 0.01$, ***, $P < 0.001$, determined by Student's *t*-test.

cells (Fig. 5B). Taken together, these data suggest that cell adhesion-mediated miR-182 up-regulation and PDCD4 down-regulation may confer drug resistance via enhancing AKT phosphorylation at Ser473.

4. Discussion

Accumulating studies have shown that dysregulation of some miRNAs may contribute to CAM-DR [15,16]. Recent studies revealed that miR-182 has a crucial role in drug resistance. Qin et al. [17] reported that upregulation of miR-182 could promote cisplatin resistance, partly by inhibiting tumor protein 53-induced nuclear protein 1 (TP53INP1) expression in HepG2 cells. Yang et al. [18] reported that aberrant microRNA-182 expression is correlated with glucocorticoid resistance in lymphoblastic malignancies via targeting FOXO3A. In addition, overexpression of miR-182 was reported to be involved in the regulation of chemoresistance of non-small cell lung cancer cells to cisplatin by down-regulating PDCD4 [11]. Furthermore, miR-182 has also been found to reduce the chemosensitivity of ovarian cancer cells to cisplatin and taxol through negatively regulating PDCD4 [12]. In this study, we demonstrated a critical role of miR-182 up-regulation in CAM-DR. Our study revealed that overexpression of miR-182 suppressed Doxo-induced cell death in both suspension and FN-adherent H929 and MM.1S cells. However, ectopic inhibition of miR-182 increased Doxo-induced cell death, and also partially abolished CAM-DR in both H929 and MM.1S cells.

PDCD4 originally acquired its name because it was induced upon programmed cell death [19]. PDCD4 also serves as a translation inhibitor. It binds with translation initiation factor 4A (eIF4A) and inhibits the helicase activity [20]. PDCD4 is ubiquitously expressed in normal human tissues [21]. Recently, PDCD4 has shown to be an oncosuppressor protein and frequently dysregulated in various malignancies, causing a disruption of the apoptotic machinery [22]. Wang et al. [23] reported that miR-320a could bind to the 3′UTR of PDCD4 mRNA, thereby mediating PDCD4 down-regulation and 5-FU resistance in human pancreatic cancer cells. In our study, silencing of PDCD4 was observed to confer resistance to Doxo-induced cell death in both suspension and FN-adherent H929 and MM.1S cells. However, ectopic expression of PDCD4 enhanced Doxo-induced cell death, and partially abolished CAM-DR in both H929 and MM.1S cells. Zhen et al. [24] reported that PDCD4 could induce miR-374a expression via the PI3K/AKT/c-JUN pathway, and the miR-374a-CCND1-pPI3K/AKT-c-JUN feedback loop induced by PDCD4 could modulate nasopharyngeal carcinoma cell growth, metastasis and cisplatin resistance. We observed that ectopic expression of miR-182 enhanced AKT phosphorylation at Ser473 in both H929 and MM.1S cells. Interestingly, similar results were observed after PDCD4 knockdown in both H929 and MM.1S cells.

In conclusion, these results suggest that cell adhesion–mediated miR-182 up-regulation and PDCD4 down-regulation may confer drug resistance via enhancing AKT phosphorylation at Ser473. Our study elucidates a potential molecular mechanism of miR-182 and PDCD4 in CAM-DR in MM.

Declaration of Competing Interest

No potential conflicts of interest were disclosed.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (81670196), Six Talent Peaks Project in Jiangsu Province (2015-WSN-097) and Pre-Research Project of Nantong University (17ZY37).

References

[1] W.I. Gonsalves, S.V. Rajkumar, V. Gupta, W.G. Morice, M.M. Timm, P.P. Singh, et al., Quantification of clonal circulating plasma cells in newly diagnosed multiple myeloma: implications for redefining high-risk myeloma, Leukemia 28 (2014) 2060–2065.
[2] J.M. Waldschmidt, A. Simon, D. Wider, S.J. Muller, M. Follo, G. Ihorst, et al., CXCL12 and CXCR7 are relevant targets to reverse cell adhesion-mediated drug resistance in multiple myeloma, Br. J. Haematol. 179 (2017) 36–49.
[3] P. Neri, L. Ren, A.K. Azab, M. Brentnall, K. Gratton, A.C. Klimowicz, et al., Integrin beta7-mediated regulation of multiple myeloma cell adhesion, migration, and invasion, Blood 117 (2011) 6202–6213.

[4] J. Kikuchi, D. Koyama, T. Wada, T. Izumi, P.O. Hofgaard, B. Bogen, et al., Phosphorylation-mediated EZH2 inactivation promotes drug resistance in multiple myeloma, J. Clin. Invest. 125 (2015) 4375–4390.
[5] Z.M. Shi, L. Wang, H. Shen, C.F. Jiang, X. Ge, D.M. Li, et al., Downregulation of miR-218 contributes to epithelial-mesenchymal transition and tumor metastasis in lung cancer by targeting Slug/ZEB2 signaling, Oncogene 36 (2017) 2577–2588.
[6] J. Abdi, H. Jian, H. Chang, Role of micro-RNAs in drug resistance of multiple myeloma, Oncotarget 7 (2016) 60723–60735.
[7] X. Wang, C. Li, S. Ju, Y. Wang, H. Wang, R. Zhong, Myeloma cell adhesion to bone marrow stromal cells confers drug resistance by microRNA-21 up-regulation, Leuk. Lymphoma 52 (2011) 1991–1998.
[8] J. Xue, A. Zhou, Y. Wu, S.A. Morris, K. Lin, S. Amin, et al., miR-182-5p induced by STAT3 activation promotes glioma tumorigenesis, Cancer Res. 76 (2016) 4293–4304.
[9] S. Zhang, Q. Zhang, G. Shi, J. Yin, MiR-182-5p regulates BCL2L12 and BCL2 expression in acute myeloid leukemia as a potential therapeutic target, Biomed. Pharmacother. 97 (2018) 1189–1194.
[10] G. Chen, L. Yu, H. Dong, Z. Liu, Y. Sun, MiR-182 enhances radioresistance in non-small cell lung cancer cells by regulating FOXO3, Clin. Exp. Pharmacol. Physiol. 46 (2019) 137–143.
[11] F.L. Ning, F. Wang, M.L. Li, Z.S. Yu, Y.Z. Hao, S.S. Chen, MicroRNA-182 modulates chemosensitivity of human non-small cell lung cancer to cisplatin by targeting PDCD4, Diagn. Pathol. 9 (2014) 143.
[12] Y.Q. Wang, R.D. Guo, R.M. Guo, W. Sheng, L.R. Yin, MicroRNA-182 promotes cell growth, invasion, and chemoresistance by targeting programmed cell death 4 (PDCD4) in human ovarian carcinomas, J. Cell. Biochem. 114 (2013) 1464–1473.
[13] X. Zhu, X. Miao, Y. Wu, C. Li, Y. Guo, Y. Liu, et al., ENO1 promotes tumor proliferation and cell adhesion mediated drug resistance (CAM-DR) in non-Hodgkin's lymphomas, Exp. Cell Res. 335 (2015) 216–223.
[14] Z.W. Li, W.S. Dalton, Tumor microenvironment and drug resistance in hematologic malignancies, Blood Rev. 20 (2006) 333–342.
[15] T. Lwin, J. Lin, Y.S. Choi, X. Zhang, L.C. Moscinski, K.L. Wright, et al., Follicular dendritic cell-dependent drug resistance of non-Hodgkin lymphoma involves cell adhesion-mediated Bim down-regulation through induction of microRNA-181a, Blood 116 (2010) 5228–5236.
[16] T. Lwin, X. Zhao, F. Cheng, X. Zhang, A. Huang, B. Shah, et al., A microenvironment-mediated c-Myc/miR-548m/HDAC6 amplification loop in non-Hodgkin B cell lymphomas, J. Clin. Invest. 123 (2013) 4612–4626.
[17] J. Qin, M. Luo, H. Qian, W. Chen, Upregulated miR-182 increases drug resistance in cisplatin-treated HCC cell by regulating TP53INP1, Gene 538 (2014) 342–347.
[18] A. Yang, J. Ma, M. Wu, W. Qin, B. Zhao, Y. Shi, et al., Aberrant microRNA-182 expression is associated with glucocorticoid resistance in lymphoblastic malignancies, Leuk. Lymphoma 53 (2012) 2465–2473.
[19] K. Zennami, S.M. Choi, R. Liao, Y. Li, W. Dinalankara, L. Marchionni, et al., PDCD4 is an androgen-repressed tumor suppressor that regulates prostate cancer growth and castration resistance, Mol. Cancer Res. 17 (2019) 618–627.
[20] Q. Wang, J. Zhu, Y.W. Wang, Y. Dai, Y.L. Wang, C. Wang, et al., Tumor suppressor Pdcd4 attenuates Sin1 translation to inhibit invasion in colon carcinoma, Oncogene 36 (2017) 6225–6234.
[21] S. Kumar, C.E. Marriott, N.F. Alhasawi, A.J. Bone, W.M. Macfarlane, The role of tumour suppressor PDCD4 in beta cell death in hypoxia, PLoS One 12 (2017) e0181235.
[22] L. Nicole, R. Cappellesso, T. Sanavia, V. Guzzardo, A. Fassina, MiR-21 over-expression and programmed cell death 4 down-regulation features malignant pleural mesothelioma, Oncotarget 9 (2018) 17300–17308.
[23] W. Wang, L. Zhao, X. Wei, L. Wang, S. Liu, Y. Yang, et al., MicroRNA-320a promotes 5-FU resistance in human pancreatic cancer cells, Sci. Rep. 6 (2016) 27641.
[24] Y. Zhen, W. Fang, M. Zhao, R. Luo, Y. Liu, Q. Fu, et al., miR-374a-CCND1-pPI3K/AKT-c-JUN feedback loop modulated by PDCD4 suppresses cell growth, metastasis, and sensitizes nasopharyngeal carcinoma to cisplatin, Oncogene 36 (2017) 275–285.