Original Article

PRDX6 promotes proliferation and induces chemo-resistance via peroxidase activity in Toledo diffuse large B-cell lymphoma cells

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Background: Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphomas. Despite the application of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen being effective on 70–80% of DLBCL patients, the remaining 20–30% develop an even more aggressive relapsed tumor. PRDX6 has been shown to play important roles in multiple cancers. However, there is no study about the role of PRDX6 in DLBCL.

Methods: The stable Toledo cell lines that overexpression or knockdown of PRDX6 gene were established. Western blot was used to determine the quantity of PRDX6 protein. Then, the function of PRDX6 in Toledo cell proliferation was determined using cell counting assay and Annexin V/PI analysis assays, and the underlying mechanism was determined through glutathione peroxidase activity and iPLA2 activity assay.

Results: In the current study, we showed that the expression of PRDX6 was critical for the proliferation of Toledo DLBCL cells. Additionally, knockdown of PRDX6 induced apoptosis in Toledo DLBCL cells. Importantly, overexpression of PRDX6 caused a doxorubicin resistance in Toledo DLBCL cells, while downregulation of PRDX6 significantly enhanced doxorubicin induced apoptosis. Interestingly, the glutathione peroxidase activity of PRDX6, but not the phospholipase A2 activity, was crucial for PRDX6 induced proliferation and anti-apoptosis effects. Together, our study explored the tumor promoting function of PRDX6 in DLBCL for the first time.

Conclusions: Our data indicated that PRDX6 could be a target for overcoming drug resistance. Targeting PRDX6 expression or peroxidase activity could be an effective strategy to overcome drug resistance in clinical DLBCL treatment.

Keywords: PRDX6; peroxidase activity; chemo-resistance; diffuse large B cell lymphoma (DLBCL)

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Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common type of B cell non-Hodgkin's lymphoma (NHL), and accounts for 30–40% of NHL cases (1). The combined chemotherapy of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has increased DLBCL survival substantially, with complete remission (CR) in approximately 80% patients (2). Although tremendous progress has been made in the outcomes of DLBCL, 30–40% of patients are refractory to treatment or relapse after initial response to therapy (3). Thus, investigating the molecular mechanisms underlying DLBCL chemo-resistance is critical for improving the treatment response.

Peroxiredoxins (PRDX) family contains six members of peroxidase (PRDX1-PRDX6). PRDX6 is a unique member of PRDXs family which displays both glutathione peroxidase and phospholipase A2 activities (4). The glutathione peroxidase activity of PRDX6 is crucial for reducing cellular H_2O_2 levels and decreasing oxidative stress-induced lipid peroxidation, membrane damage, and apoptosis (5-7). The phospholipase A2 activity of PRDX6 catalyzes the hydrolysis of the sn-2 fatty acyl ester bond of glycerophospholipids to produce free fatty acids and lysophospholipids, and is critical in phospholipid metabolism and cell signaling (8). Recent evidence suggests that PRDX6 plays important roles in multiple cancers. For example, PRDX6 is upregulated in cancerous hepatoma cell line compared with noncancerous counterpart. The anti-oxidant activity of PRDX6 suppresses peroxide-induced cytotoxicity in hepatoma cell (9). Additionally, the phospholipase A2 activity of PRDX6 is important for PRDX6 promoted proliferation and induction of Src family kinase activation in melanoma cells (10). Moreover, PRDX6 also promotes invasion and metastasis in lung cancer cells via its phospholipase A2 activity (11). However, little is known about the role of PRDX6 in DLBCL, and the underlying molecular mechanism is largely unknown.

In current study, we evaluate the functions of PRDX6 in DLBCL, and demonstrate the potential molecular mechanism behind it. We found that overexpression of PRDX6 significantly promoted proliferation of Toledo DLBCL cells, while downregulation of PRDX6 suppressed the proliferation. Additionally, downregulating the expression of PRDX6 induced apoptosis in Toledo DLBCL cells. Importantly, our data showed that upregulation of PRDX6 alleviated doxorubicin induced apoptosis, while downregulation of PRDX6 produced a synergistic effect on apoptosis when Toledo DLBCL cells treated with doxorubicin. Mechanically, PRDX6 displayed both glutathione peroxidase and phospholipase A2 activities in Toledo DLBCL cells. Interestingly, inhibition of glutathione peroxidase activity of PRDX6 by M-succinate (mercaptosuccinate) treatment reversed PRDX6 promoted proliferation and anti-apoptosis effects, while inhibition of phospholipase A2 activity did not. Our data indicated that PRDX6 was a critical molecule to induce doxorubicin resistance, targeting the glutathione peroxidase activity of PRDX6 could be a promising strategy to overcome doxorubicin resistance.

Methods

Reagents and cells culture

Doxorubicin and Annexin V-FITC Apoptosis Detection Kit were purchased from Sigma-Aldrich. Flag, PRDX6, and GAPDH were purchased from Cell Signaling Technology. Toledo was obtained from the American Type Culture Collection (ATCC) and was cultured in RPMI-1640 (Gibco) supplemented with 10% fetal bovine serum (FBS; Hyclone). Cells were maintained at 37 ℃ in a humidified 5% CO_2 atmosphere.

shPRDX6 stable cell lines established

Knockdown of gene was performed with the specific shRNA delivered by a lentiviral system purchased from Sigma-Aldrich Corp, according to the instruction manual. 293T cells were co-transfected with pMD2. G and psPAX2 compatible packaging plasmids and pLKO.1 plasmid bearing the specific shRNA for 24 h. The cultured medium containing lentivirus was collected. Then Toledo cells were infected with the lentivirus bearing the shRNA in growth medium containing 8 μg/mL polybrene for 24 h. Afterwards, cells were subcultured and selected with 2 μg/mL puromycin. The shRNA constructs targeting the gene and referring to the sequence is: PRDX6 (NM_004905.2): TRCN0000052154 (5'-CCGGCCGAAAGGAGTCTTCACCAAACTCGAG TTTGGTGAAGACTCCTTTCGGTTTTTG-3').

PRDX6-flag overexpressed stable cell lines established

The plasmids encoding PRDX6 was generated by PCR amplification and subcloned into the pLVX-DsRed-

Monomer-N1 expression vector. The primers for gene PRDX6-flag cloning were as follow: 5'-AACTCGAGATGCCCGGAGGTCTGCTTCTC-3'; 5'-AAGAATTCTTACTTATCGTCGTCATCCTTGTAATCAGGCTGGGGTGTGTAGCGGAG-3'. 5×10^6 293T cells were transfected with lentiviral vector, psPAX2 and pMD2.G. Supernatants were collected every 24 h between 24 to 72 h after transfection, pulled together and concentrated via ultracentrifugation, and the viral titer was determined by serial dilutions. The multiplicity of infection during transfection was 10. 2×10^5 cell were treated with polybrene (8 μg/mL) and virus contained supernatants for 24 h. Cells were growth for another 48h. Cells were treated with puromycin (2 μg/mL) for 72 h to establish stable cells.

Small interfering RNA transfection

Toledo cells were seeded in six-well plates. In each well, 100 nM of siRNA and 5 μL of Lipofectamine 2000 were added to Opti-MEM, mixed and then added to the cells. After transfection of siRNAs for 24 or 48 h, RNAi efficiency was determined by western blot. The siRNA was purchased from GenePharma company and the sequence was as follow: si-PRDX6 5'-CCGAAAGGAGTCTTCACCAAA-3'.

Cell counting assay

About 1×10^5 cells per well were plated in six-well plates. Subsequently, cells were treated. Then, cell count was determined with trypan blue exclusion assay.

Annexin V/PI analysis

Cells treated with indicated concentration of indicated drug for indicated time. Cells were collected and resuspended in the binding buffer (500 μL/sample). Annexin-V-FITC (5 μL/sample) was added to the cells followed by addition of 5 μL/sample PI (propidium iodide). The samples were then incubated for 15 min in the dark at 4 ℃ and subjected to flow cytometry analysis (12).

Western blot analysis

Cells were harvested and lysed in RIPA buffer. The protein concentration was determined by Bradford method with BSA (Sigma) as the standard. Equal amounts of cell extract were subjected to electrophoresis in SDS-polyacrylamide gel and transferred to nitrocellulose membrane (Millipore). The membranes were blocked and then incubated with flag, PRDX6 and GAPDH (Cell Signaling Technology Corp, Beverly, MA, USA) antibodies at 4 ℃ overnight, followed by incubation for 1 h room temperature with appropriate secondary antibodies. Antibody binding was detected with an enhanced chemiluminescence kit (Pierce).

Glutathione peroxidase activity and iPLA2 activity assay

Glutathione peroxidase assay (No. 703102) and cPLA2 assay kits (No. 765021) were purchased from Cayman Chemical and iPLA2 and glutathione peroxidase activities were measured according to the manufacturer's recommendations (13).

Statistics

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc.) and GraphPad Prism 6 (GraphPad Software, Inc.). The Student's *t* test and multi-factorial ANOVA were used to make a statistical comparison. The level of significance was set at $P<0.05$.

Results

PRDX6 is critical for cell proliferation in Toledo DLBCL cells

To study the functions of PRDX6 in DLBCL, we evaluated the proliferation of Toledo DLBCL cells at first. We established a stable PRDX6-flag overexpressed cell line (PRDX6 cells) and the control cell line (Vec cells, vector cell) in Toledo DLBCL cells by lentivirus mediated gene transfer. Western blot analysis showed that PRDX6 cells indeed overexpressed PRDX6-flag protein (*Figure 1A*). We then evaluated proliferation by cell counting assay. As shown in *Figure 1B*, PRDX6 cells displayed a significant advantage in cell proliferation as compared with Vec cells. To further confirm the effect on proliferation, we established another stable cell line expressed PRDX6 shRNA (shPRDX6 cells) and the control cell line (NC cells, negative control cells) in Toledo DLBCL cells by lentivirus mediated gene transfer. The expression of PRDX6 was down regulated up to approximately 70% in shPRDX6 cells as compared with NC cells (*Figure 1B*). The proliferation of Toledo DLBCL cells was significantly suppressed by downregulation of PRDX6 (*Figure 1B*). These data indicated that PRDX6 has an important role in regulating the proliferation of Toledo DLBCL cells.

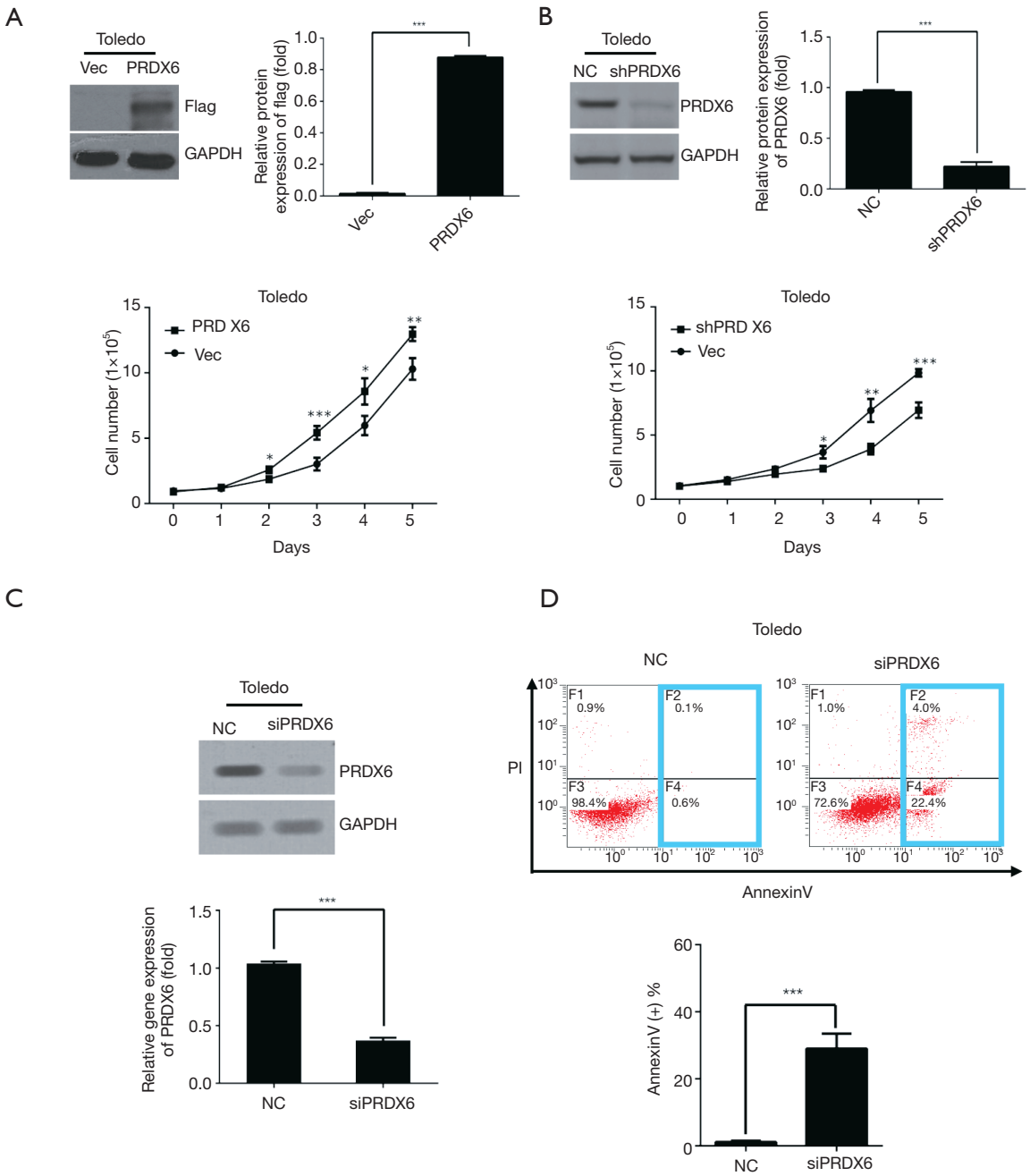

Figure 1 Effect of PRDX6 on Toledo DLBCL cells growth. (A) PRDX6-flag (PRDX6 cells) was stably expressed in Toledo cells by lentivirus mediated transfection. 3×10^6 of PRDX6 cells or control cells (Vec) were subjected for western analysis and relation protein quantification was showed. 1×10^5 of PRDX6 cells or control cells (Vec) were seeded in 6-well plate. For each day, three well of cell in each group were analyzed by cell counting assay. The data from three independent experiments were drawn a line graph. (B) PRDX6 shRNA (shPRDX6 cells) was stably expressed in Toledo cells by lentivirus mediated transfection. 3×10^6 of shPRDX6 cells or control cells (NC) were subjected for western analysis, and relation protein quantification was showed. 1×10^5 of shPRDX6 cells or control cells (NC) were seeded in 6-well plate. For each day, three well of cell in each group were analyzed by cell counting assay. The data from three independent experiments were drawn a line graph. (C) PRDX6 was knocked down by siRNA in Toledo cells (3×10^6). The Western blot was showed. (D) After 48h, cells knocked down by siRNA were collected for apoptosis analysis by testing with flow cytometry. The bar represents means ± SD of three independent experiments (*, P<0.05; **, P<0.01; ***P, <0.001). DLBCL, diffuse large B cell lymphoma.

Downregulation of PRDX6 induces apoptosis in Toledo DLBCL cells

We next evaluated the effect of PRDX6 on apoptosis. As shown in *Figure S1*, upregulation of PRDX6 did not induce apoptosis in Toledo DLBCL cells. However, downregulating the expression of PRDX6 by siRNA induced a substantial apoptosis in Toledo DLBCL cells (*Figure 1C*,*D*). The population of apoptotic cell were 28.97%±3.70% (P<0.001) in siPRDX6 cells and 1.13%±0.33% in NC cells.

PRDX6 induces chemo-resistance in Toledo DLBCL cells

Chemo-resistance is the main obstacle faced in DLBCL treatment. We further detected whether PRDX6 might affect the sensitivity of DLBCL cells to doxorubicin, an important component in R-CHOP regimen. As shown in *Figure 2*, 0.2 μM doxorubicin treatment (Dox) significantly induced apoptosis in Toledo DLBCL cells (comparing the first and third panel of *Figure 2A* up, comparing the first and third column of *Figure 2B* left). The apoptosis populations in control group and Dox group were 2.07%±0.41% and 49.90%±2.74% (P<0.001) respectively. However, overexpression of PRDX6 markedly reduced doxorubicin induced apoptosis (comparing the third and fourth panel of *Figure 2A* up, comparing the third and fourth column of *Figure 2B* left). The apoptosis populations in Dox group and Dox+ group were 49.90%±2.74% and 16.07%±1.83% (P<0.001) respectively.

Downregulation of PRDX6 enhances Dox induced apoptosis in Toledo DLBCL cells

We next examined the effect of PRDX6 downregulation on Dox induced apoptosis. As shown in *Figure 2A* down and 2B right, we treated Toledo with 0.05 μM doxorubicin to induce a moderate level of apoptosis. Low concentration of doxorubicin treatment induced 23.17%±2.00% (P<0.001) level of apoptosis as comparing with 2.36%±0.63% in control group (comparing the first and third panel of *Figure 2A* down, comparing the first and third column of *Figure 2B* right). Downregulation of PRDX6 expression by siRNA also induced a moderate level of apoptosis (23.17%±2.00%). Interestingly, downregulation of PRDX6 expression substantially increased doxorubicin induced apoptosis (*Figure 2A* down and *2B* right). The level of apoptosis in the combined group was 90.00%±3.47% which was significantly higher than the apoptosis of Dox group plus siPRDX6 group (*Figure 2A* down and *Figure 2B* right). These data suggested that siPRDX6 might induce a synergetic apoptosis effect when combining with doxorubicin treatment.

Peroxidase activity is responsible for PRDX6 induced cell growth and anti-apoptotic effects in Toledo DLBCL cells

Since PRDX6 displays both glutathione peroxidase and phospholipase A2 (iPLA2) activities (4). We further examined which activity was responsible for PRDX6 induced proliferation and anti-apoptosis. We upregulated or downregulated PRDX6 expression in a dose-dependent manner by transient transfection. As shown in *Figure 3A*,*B*, the glutathione peroxidase and iPLA2 activities were gradually increased as the PRDX6 expression increasing. Conversely, the glutathione peroxidase and iPLA2 activities were gradually suppressed as the PRDX6 expression decreasing (*Figure 3C*,*D*). We then inhibited the glutathione peroxidase or iPLA2 activities by M-succinate (mercaptosuccinate) or MJ33 respectively (4,14). As shown in *Figure 4A*, M-succinate effectively reversed PRDX6 induced proliferation, but MJ33 did not. As shown in *Figure 4B*,*C*, PRDX6 alleviated Dox induced apoptosis. However, M-succinate, but not MJ33, overcame PRDX6 induced Dox resistance (*Figure 4B*,*C*). These data indicated that the glutathione peroxidase activity was critical for PRDX6 induced proliferation and Dox resistance.

Discussion

In the current study, we explored the function of PRDX6 in DLBCL cells. Our data showed PRDX6 is critical for the proliferation of Toledo DLBCL cells. Additionally, overexpression of PRDX6 conferred Dox-resistance to Toledo DLBCL cells. Moreover, combination of Dox treatment and siPRDX6 induced a synergetic effect on apoptosis. Mechanically, we showed that inhibition of glutathione peroxidase activity of PRDX6 by M-succinate, but not inhibition of phospholipase A2 activity of PRDX6 by MJ33, overcame PDRX6 induced proliferation and anti-apoptosis effects.

DLBCL is a kind of aggressive lymphoma which composes of large, transformed B cells, and displays in diffuse growth pattern (15). The addition of rituximab to CHOP regimen generated a significant improvement in DLBCL treatment in two decades. Although the prognosis of DLBCL has been improved significantly, resistance

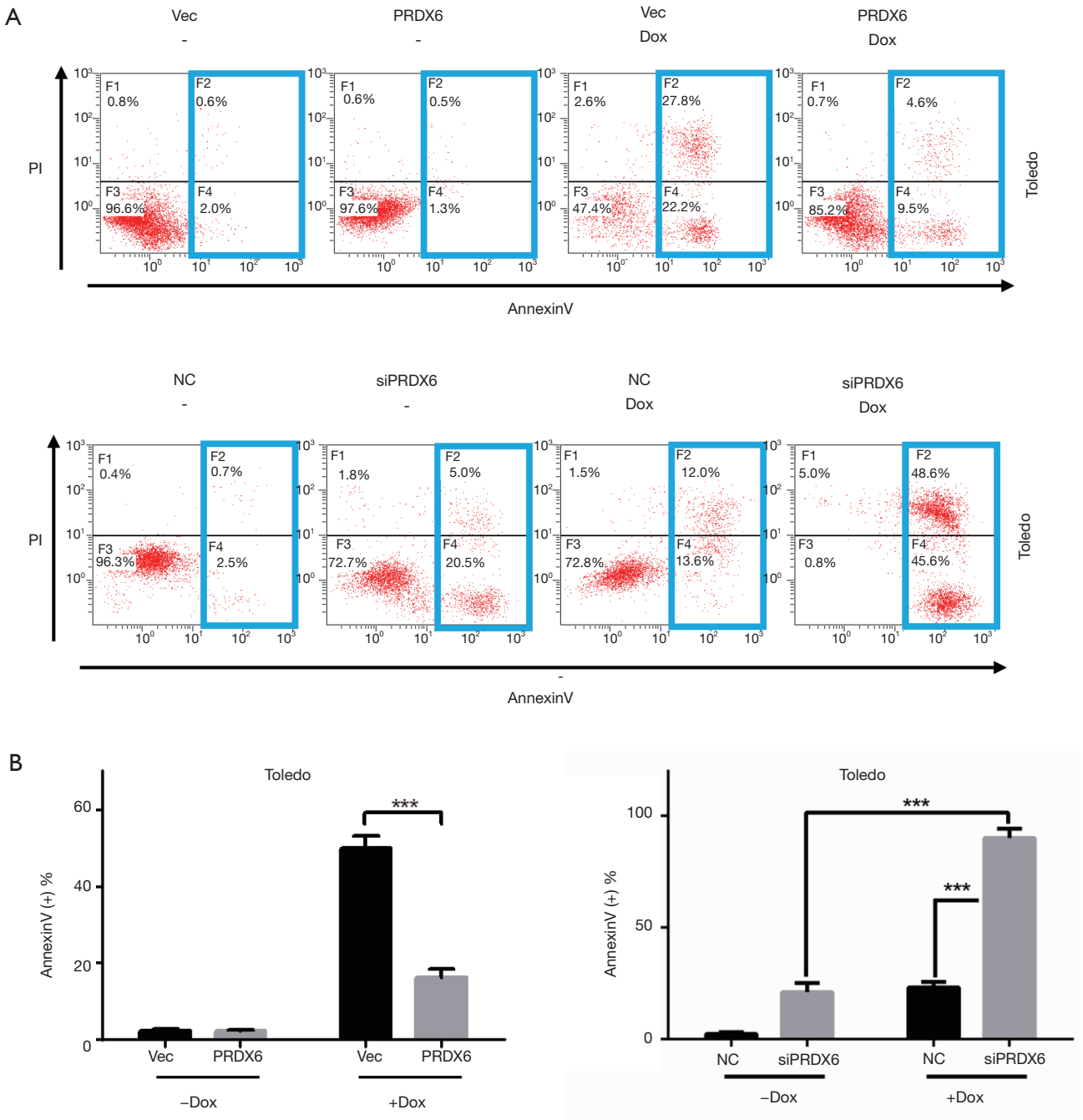

Figure 2 PRDX6 induces chemo-resistance and downregulation of PRDX6 enhances Dox induced apoptosis in Toledo DLBCL cells. (A) (up) Two sets of PRDX6 (2×10^6) cells and Vec cells (2×10^6) were seeded. One set of cells was treated with control reagent, the other set was treated with 0.2 μM doxorubicin for 48 h. Then, cells were collected for apoptosis analysis. (down) Four sets of Toledo (2×10^6) cells were seeded. These sets of cells were treated with control reagent plus non-specific siRNA, control reagent plus PRDX6 specific siRNA, 0.05 μM doxorubicin plus non-specific siRNA or 0.05 μM doxorubicin plus PRDX6 specific siRNA for 48 h. Then, cells were collected for apoptosis analysis. (B) The data from three independent experiments were drawn a histogram. The bar represents means ± SD of three independent experiments (***, P<0.001).

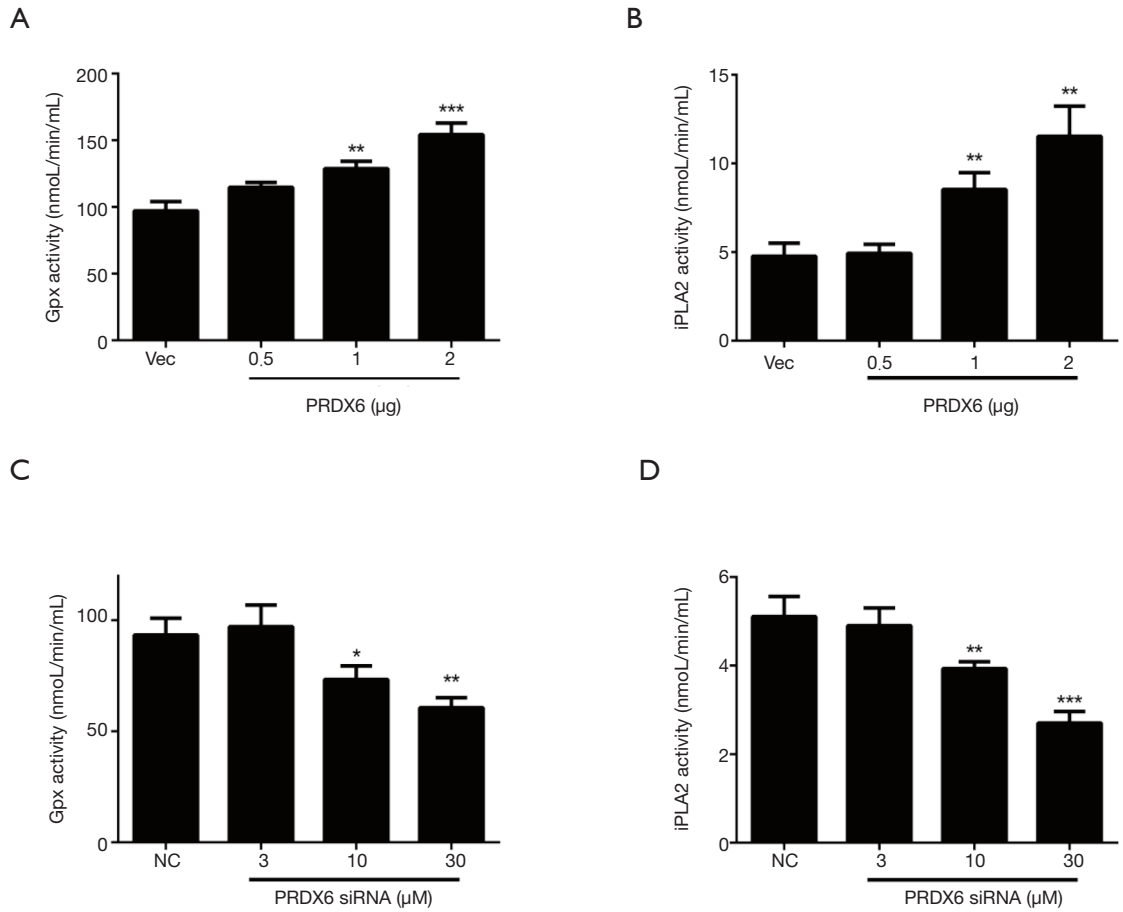

Figure 3 PRDX6 activates glutathione peroxidase and iPLA2 in Toledo DLBCL cells. (A and B). Toledo (2×10^6) cells were transiently transfected with indicated amount of plasmid expressed PRDX6-flag. After 48 h, cells were collected for glutathione peroxidase (A) or iPLA2 activities analysis (B). (C and D) Toledo (2×10^6) cells were transiently transfected with indicated amount of non-specific siRNA or siRNA against PRDX6. After 48 h, cells were collected for glutathione peroxidase (C) or iPLA2 activities analysis (D). DLBCL, diffuse large B cell lymphoma. *, P<0.05; **, P<0.01; ***, P<0.001.

to the CHOP regimen continues to pose a problem in managing or curing DLBCL (16). Thus, elucidating the mechanism of chemo-resistance and identifying new therapeutic target are urgently needed to improve the quality of patient care and effectiveness of CHOP therapies. In this study, we focused on doxorubicin resistance in DLBCL, which is a main component of CHOP regimen. We showed that PRDX6 expression was critical for inducing doxorubicin resistance. Targeting PRDX6 not only overcame doxorubicin resistance, but also produced a synergetic effect on apoptosis in Toledo DLBCL cells.

PRDX6 is a member of the family of non-selenium thiol peroxidases. Recent studies have shown that PRDX6 are up-regulated in various cancers, including breast cancer (17), lung cancer (18) or tongue squamous cell carcinoma (19). However, there is no study about the function of PRDX6 in DLBCL. We studied the effects of PRDX6 on cell proliferation, apoptosis and drug resistance in DLBCL for the first time. Our data showed that the expression of PRDX6 was important for the cell proliferation and apoptosis in Toledo DLBCL cells. More importantly, PRDX6 was a crucial molecule mediated doxorubicin resistance. Targeting PRDX6 by siRNA produced synergetic effect on apoptosis when combined with doxorubicin treatment. These data suggested a promising therapeutic potential of PRDX6 in clinical treatment of DLBCL.

PRDX6 is a unique bifunctional enzyme in PRDX

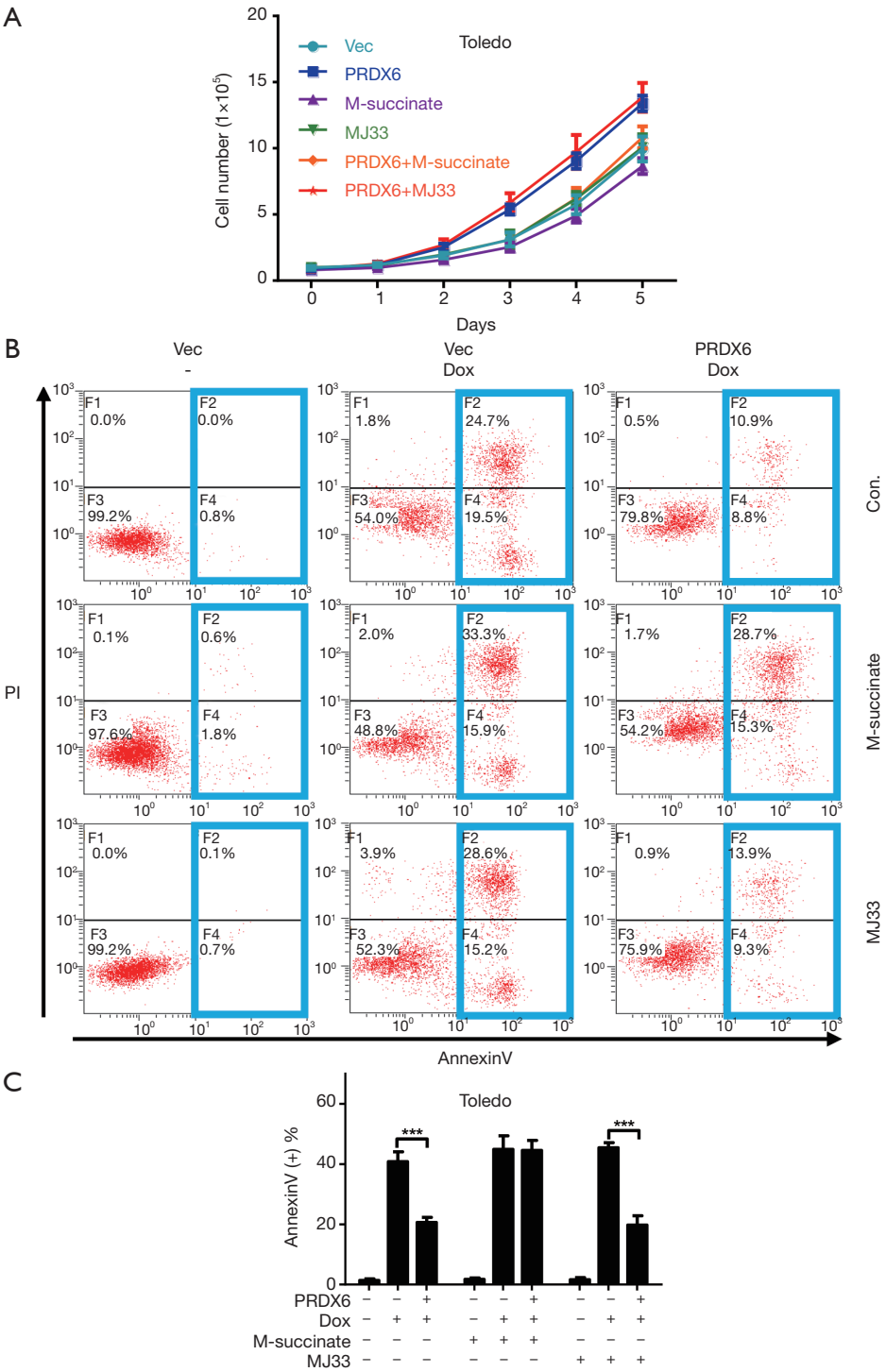

Figure 4 Peroxidase activity is responsible for PRDX6 induced cell growth and anti-apoptotic effects in Toledo DLBCL cells. (A) Three sets of PRDX6 (2×10^6) cells and Vec cells (2×10^6) were seeded. These sets of cells were treated with control reagent, M-succinate (20 μM) or MJ33 (10 μM) for indicated time. Cells were collected for cell number counting. The data from three independent experiments were drawn a line graph. (B) The experiment settings were similar with (A). After 48 h, cells were collected for apoptosis analysis. The representative results were shown. (C) The data from three independent experiments of (B) were drawn a histogram. The bar represents means ± SD of three independent experiments (***, P<0.001).

family that contains, in addition to its peroxidase activity, iPLA2 activity (4). Previous studies indicated that the peroxidase activity and iPLA2 activity might have different function. For example, the peroxidase activity of PRDX6 was important for cell growth. This effect could be blocked by M-succinate, which was a peroxidase activity inhibitor, but not MJ33, which was a iPLA2 activity inhibitor (11). Conversely, the invasion ability was mainly supported by iPLA2 activity (11). Consistently, our study supported that PRDX6 promoted Toledo DLBCL cells proliferation via peroxidase activity. Importantly, we showed that the anti-apoptosis function of PRDX6 was also supported by peroxidase activity, but not iPLA2 activity. These data indicated that inhibition of PRDX6 peroxidase activity might also an effective strategy to overcome PRDX6 induced drug resistance in DLBCL.

Together, our study explored the tumor promoting function of PRDX6 in DLBCL. Our data implied that PRDX6 was a crucial factor to induce drug resistance. Targeting PRDX6 expression or peroxidase activity could be an effective strategy to overcome drug resistance in clinical DLBCL treatment.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.08.36). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The institutional ethical approval and individual informed consent were waived.

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Supplementary

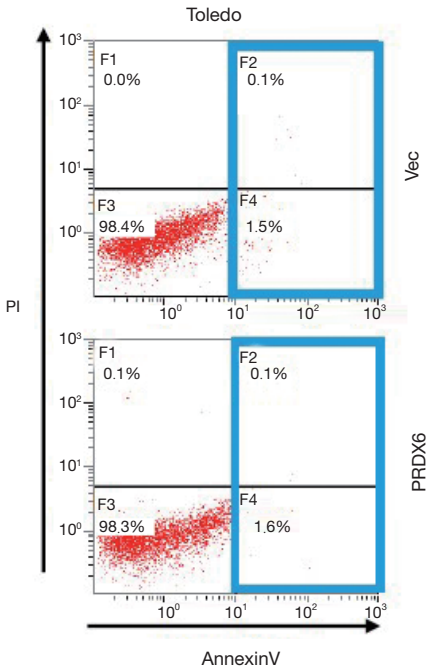

Figure S1 Upregulation of PRDX6 does not induce apoptosis in Toledo DLBCL cells. DLBCL, diffuse large B cell lymphoma.