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PRMT1 is an important factor for medulloblastoma cell proliferation and survival

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ABSTRACT

Aberrant expression of protein arginine methyltransferases (PRMTs) has been implicated in a number of brain tumors, but the role of PRMT1 in medulloblastoma, the most common malignant pediatric brain tumor, remains unexplored. By examining the publicly available databases of pediatric brain tumor collection, we found that PRMT1 was predominantly expressed in medulloblastomas across all the pediatric brain tumors and that the high-level expression of PRMT1 correlated with poor survival of medulloblastoma patients. To determine the role of PRMT1 in medulloblastoma cells, we established an inducible knockdown system and demonstrated that PRMT1 depletion decreased medulloblastoma cell proliferation and induced cell apoptosis. Furthermore, the diamidine compounds, previously shown to exhibit selective PRMT1 inhibition, suppressed medulloblastoma cell viability in a dose-dependent manner. Finally, we observed induction of medulloblastoma cell apoptosis by the potent diamidine compounds at low micromolar concentrations. Together, our results suggest that PRMT1 could be an actionable therapeutic target in medulloblastoma.

1. Introduction

Protein arginine methylation, catalyzed by protein arginine methyltransferases (PRMTs), is an abundant post-translational modification involved in various essential cellular processes. Emerging evidence has linked alterations in PRMTs to a variety of cancers, including brain tumors [1]. Thus, PRMTs may represent attractive targets for cancer therapy. Medulloblastoma, the most common malignant childhood brain tumor of the cerebellum, accounts for about 20% of all pediatric brain tumors [2]. But the role of PRMTs in the development of medulloblastoma remains largely unexplored.

PRMT1 and PRMT5 are the predominant type I and II PRMTs that catalyze most asymmetrical di-methylarginine and symmetrical di-methylarginine marks, respectively. PRMT5 was the first PRMT to be targeted in clinical trials for brain tumors [1]. A recent report identified PRMT5 as a critical regulator of expression of MYC, an oncoprotein that drives the pathogenesis of *MYC*-amplified Group 3 medulloblastomas [3]. Furthermore, this study showed dose-dependent efficacy of a PRMT5 inhibitor in MYC-driven medulloblastoma cell culture [3]. We have previously revealed an essential role of PRMT1 in promoting neuroblastoma cell survival, as well as anti-neuroblastoma effects of diamidine-related PRMT1 inhibitors in both cell culture and in tumor-bearing mice [4]. PRMT1 has been implicated in cerebellar tumorigenesis and development of medulloblastoma [5], but to our

Abbreviations: Dox, Doxycycline; PRMT1, protein arginine methyltransferase 1; shRNA, short hairpin RNA.

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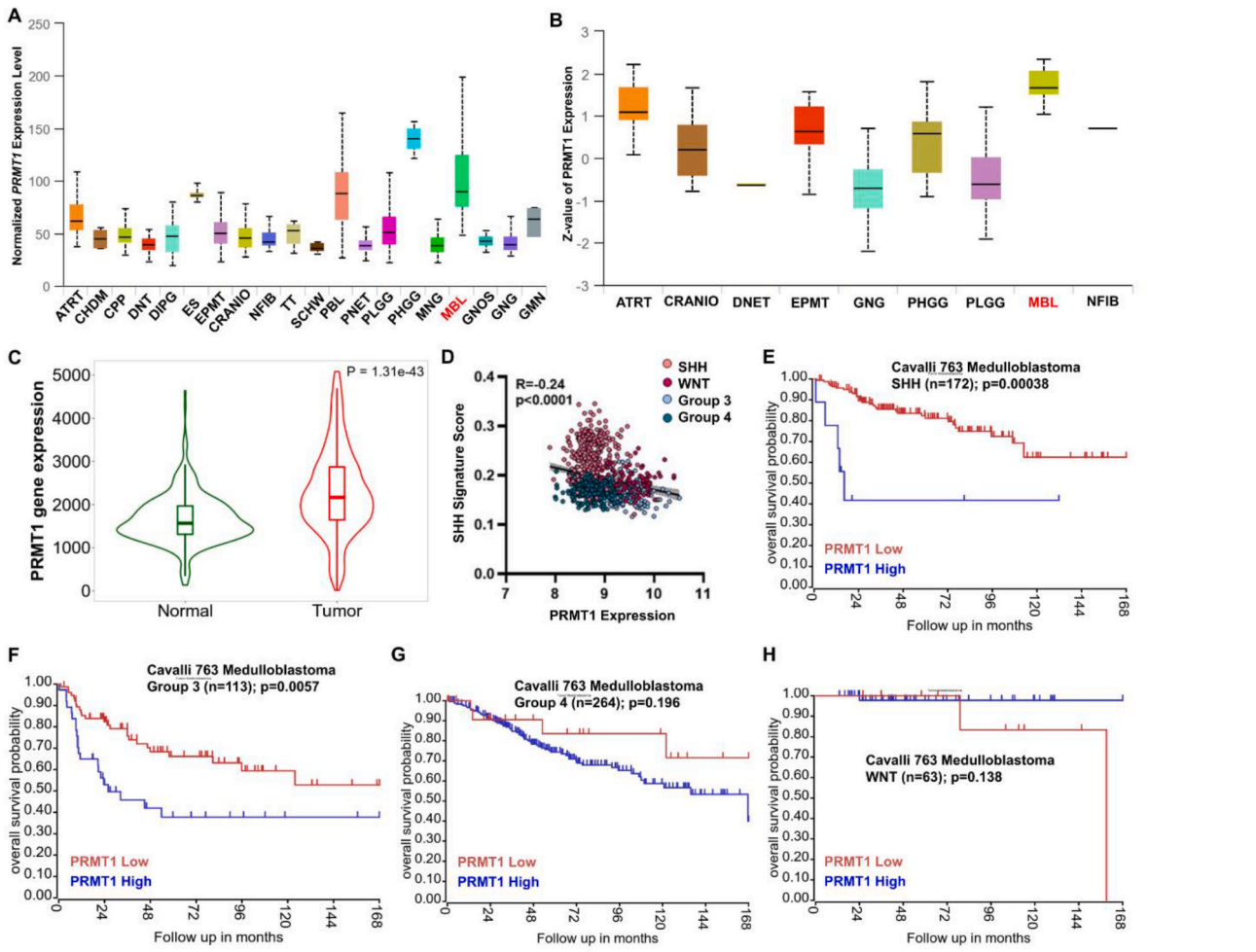

Fig. 1. PRMT1 expression and correlation in human medulloblastoma tumors. (A), Normalized PRMT1 mRNA expression level across pediatric brain tumors in CBTTC dataset in UALCAN (http://ualcan.path.uab.edu/analysis-cbttc.html), with medulloblastoma shown in red. **(B),** Z-value of PRMT1 protein expression across pediatric brain tumors in CBTTC dataset in UALCAN (http://ualcan.path.uab.edu/analysis-cbttc.html), with medulloblastoma shown in red. The Z-values of PRMT1 expression represent standard deviations from the median across samples for the given tumor type. **(C),** PRMT1 mRNA expression in brain tumors vs normal brain tissues. Data was analyzed by using TNMplot: differential gene expression analysis in Tumor, Normal and Metastatic tissues (https://tnmplot.com/analysis/). **(D)** Correlation between PRMT1 and SHH signature score in medulloblastoma dataset GSE85212 (n = 763). **(E–H),** Correlation of PRMT1 mRNA expression with patient survival of medulloblastoma (Cavalli 763 cohort). Kaplan-Meier plots showing overall survival of patients with SHH **(E),** Group 3 **(F),** Group 4 **(G),** and WNT **(H)** with respect to PRMT1 mRNA expression. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

knowledge, the direct role of PRMT1 in medulloblastoma cells has not been investigated. In the present study, we define the correlation of PRMT1 expression with medulloblastoma patient survival, examine the role of PRMT1 in medulloblastoma cell growth and survival, and test the efficacy of diamidine-related PRMT1 inhibitors in medulloblastoma cells.

2. Materials and methods

2.1. Patient data acquisition

The expression of PRMT1 mRNA in pediatric brain tumors was analyzed using data from the Children Brain Tumor Tissue Consortium (CBTTC) dataset in UALCAN (http://ualcan.path.uab.edu/analysis-cbttc.html) [6]. The Z-values of PRMT1 protein expression represent standard deviations from the median across samples for the given tumor type. Log2 Spectral count ratio values from the Clinical Proteomic Tumor Analysis Consortium (CPTAC) database were first normalized within each sample profile, then normalized across samples.

The differential analysis of PRMT1 mRNA expression in brain tumors vs normal brain tissues was performed by using TNMplot: differential gene expression analysis in Tumor, Normal and Metastatic tissues (https://tnmplot.com/analysis/) [7].

Sonic Hedgehog (SHH) signature score was calculated as geometric mean gene expression from SHH signaling (BioCarta-Online maps of metabolic and signaling pathway, https://www.hsls.pitt.edu/obrc/index.php?page=URL1151008585). Pearson correlation was calculated for PRMT1 and SHH signature score by using medulloblastoma dataset GSE85212 (n = 763). SHH gene set was from http://www.gsea-msigdb.org/gsea/msigdb/cards/BIOCARTA_SHH_PATHWAY.html.

The correlation of PRMT1 mRNA expression with patient survival across medulloblastoma subgroups was analyzed using the R2 Genomic Analysis and Visualization Platform (https://hgserver1.amc.nl/cgi-bin/r2/main.cgi).

2.2. Cell culture and reagents

Human medulloblastoma cell lines DAOY and D283 were generously provided by Dr. Rakesh K. Singh (University of Rochester Medical Center). Cells were routinely maintained in Dulbecco's Modified Eagle's Medium (DMEM; Thermo Fisher Scientific #11965092) with 10% fetal bovine serum and 100 units/mL penicillin/0.1 mg/mL streptomycin.

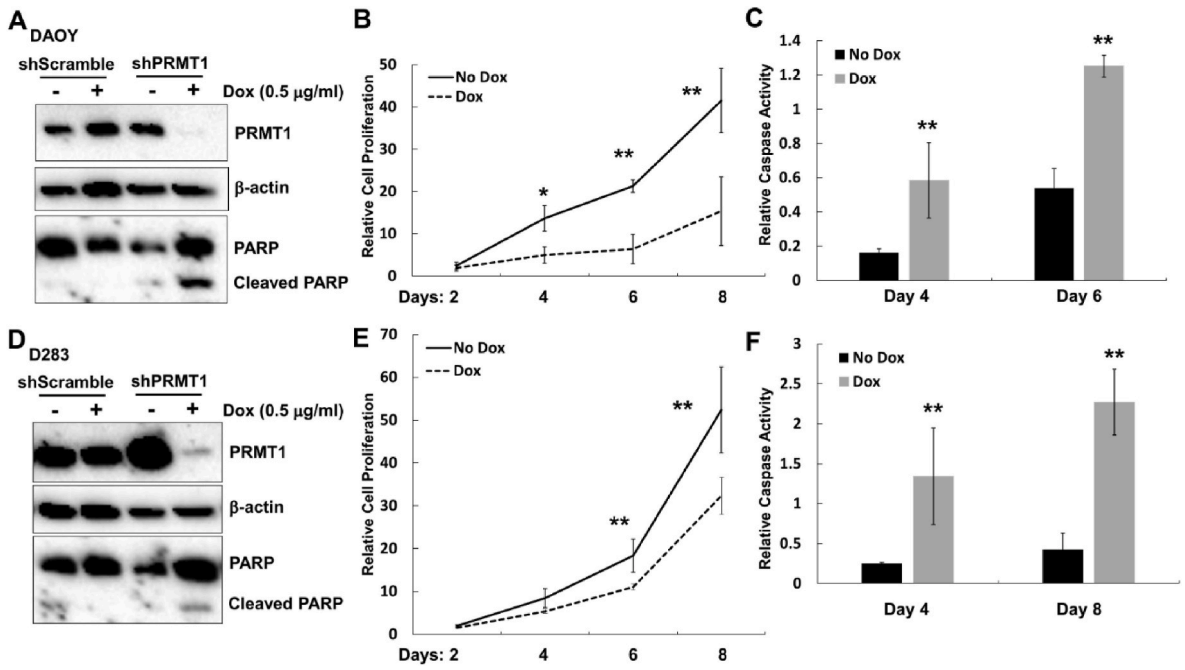

Fig. 2. PRMT1 is essential for the proliferation and survival of human medulloblastoma cells. (A), Western blot showing the expression of PRMT1 and PARP in DAOY cells stably expressing Dox-inducible shRNA targeting PRMT1 or scramble. **(B),** PRMT1 depletion suppressed DAOY cell proliferation. Data are mean ± SD (n = 3) relative to scramble without Dox (100%). **(C),** Caspase-3/7 activity assay in DAOY shPRMT1 cells with or without Dox. Data are mean ± SD (n = 3) relative to cells without Dox. **(D),** Western blot showing the expression of PRMT1 and PARP in D283 cells stably expressing Dox-inducible shRNA targeting PRMT1 or scramble. **(E),** PRMT1 depletion suppressed D283 cell proliferation. Data are mean ± SD (n = 3) relative to scramble without Dox (100%). **(F),** Caspase-3/7 activity assay in D283 shPRMT1 cells with or without Dox. Data are mean ± SD (n = 3) relative to cells without Dox. Student t-test. *: $P < 0.05$. **: $P < 0.01$.

Cells were cultured in standard humidified Carbon Dioxide (CO2) incubator set to 5% CO2. Cell viability and cell proliferation were performed by using alamarBlue Cell Viability Reagent (Thermo Fisher Scientific #DAL1025) and trypan blue (Thermo Fisher Scientific #15250061) staining as previously described [4]. Caspase-3/7 activities were detected using a Caspase-Glo 3/7 Assay System (Promega #G8091) according to the manufacturer's instruction. AlamarBlue cell viability assay was performed in parallel to control for the differences in the cell number.

Furamidine dihydrochloride (Tocris Bioscience #5202) was purchased from Tocris. Pentamidine isethionate (Sigma P0547) and hexamidine diisethionate (Sigma #H0330000) were purchased from Sigma. Decamidine was described previously [4]. Doxycycline hyclate (Sigma #D9891) was obtained from Sigma.

2.3. Inducible knockdown

The inducible PRMT1 knockdown cells were generated essentially as previously described [4]. Briefly, shPRMT1 sequences were cloned into pTRIPZ inducible shRNA lentiviral vector. The infectious lentiviruses carrying pTRIPZ-shPRMT1 were produced in 293T cells by calcium phosphate transfection. DAOY and D283 cells were infected with pTRIPZ-shPRMT1 lentivirus in the presence of 8 μg/mL of Polybrene (Santa Cruz #sc-134220). Cells were then selected with 1 μg/mL puromycin 24 h post-infection.

2.4. Immunoblotting

Whole cell lysates were isolated as described by Hua et al. [4]. A total of 20 μg of whole cell lysates was loaded onto 10% polyacrylamide gel and separated by Tris/glycine sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). After transfer and blocking with Blocking One blocking buffer (nacalai tesque, INC #03953-95), the primary antibodies were incubated with the membrane overnight at 4 °C with gentle rocking, followed by incubation with secondary antibodies for 1 h at room temperature. Finally, proteins were detected using SuperSignal West Dura Extended Duration Substrate (Thermo Fisher Scientific; #34075). Antibodies and the dilution of each antibody used for immunoblotting were: anti-PRMT1 (Millipore #07–404; 1:2000), anti-PARP (Cell Signaling #9532S; 1:1000) and β-actin (Sigma #A5441; 1:5000).

2.5. Statistical analysis

All experiments were repeated at least three times and data were presented as mean ± standard derivation (SD). Statistical differences were calculated using independent Student t-tests or analysis of variance (ANOVA). *P*-values of <0.05 (*) and <0.01 (**) were considered statistically significant. The IC50 values of diamidine compounds for each cell line were determined using GraphPad Prism V6 software.

3. Results and discussion

3.1. High levels of PRMT1 correlated with poor survival of medulloblastoma patients

PRMT1, the predominant type I PRMT, accounts for more than 80% of cellular PRMT activity [8]. Aberrant expression of PRMT1 has been implicated in the tumorigenesis of multiple brain tumors, including glioma and glioblastoma [1]. But the expression and function of PRMT1 in medulloblastoma have not been directly investigated. We first asked if PRMT1 expression is altered in pediatric brain tumors by analyzing its mRNA levels in 948 pediatric brain tumors from the Children Brain Tumor Tissue Consortium (CBTTC) dataset in UALCAN (http://ualcan.path.uab.edu/analysis-cbttc.html) [6]. We found that medulloblastoma was the predominant tumor type with high mRNA level of PRMT1 across 20 pediatric brain tumor types (Fig. 1A; for the detailed description of these 20 pediatric brain tumor types, see Supplemental

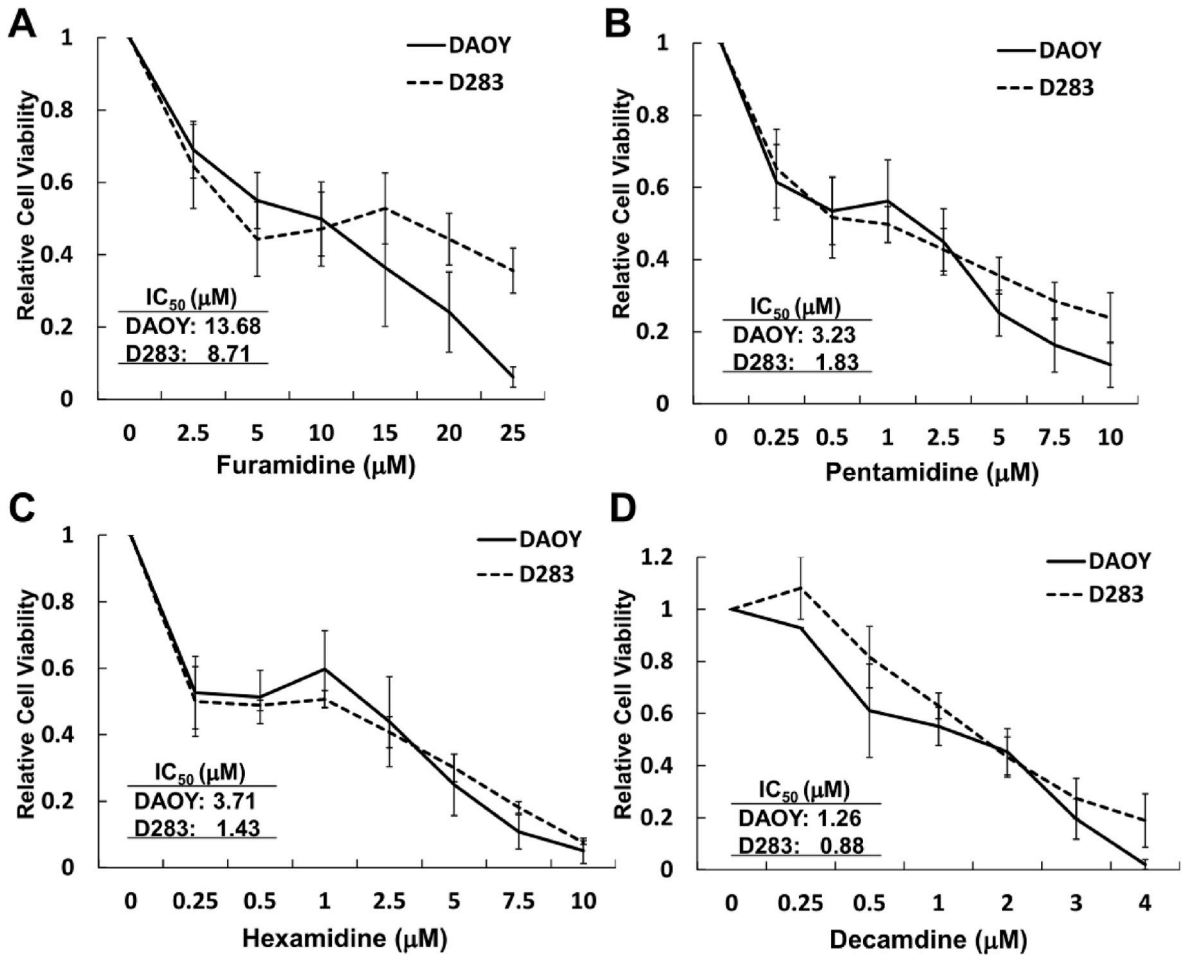

Fig. 3. Diamidine compounds reduced cell growth in human medulloblastoma cells. Cell viability of human medulloblastoma cells treated with indicated compounds for 2 days (**A**, furamidine; **B**, pentamidine; **C**, hexamidine; and **D**, decamidine), as determined by using Alamar blue assay. Data are mean ± SD (n ≥ 3) relative to DMSO control (100%). IC50 values shown for individual compounds for DAOY and D283 cells were determined using GraphPad Prism V6 software.

Table 1). Importantly, our analysis of the protein expression of PRMT1 in 198 pediatric brain tumors showed high-level of PRMT1 protein in medulloblastoma among 9 pediatric tumor types (Fig. 1B; for the detailed description of these 9 pediatric brain tumor types, see Supplemental Table 1). Importantly, differential gene expression analysis in tumor and normal tissues in the TNMplot database [7] indicated a significantly higher level of PRMT1 mRNA in tumors as compared to normal brain tissues (Fig. 1C; https://tnmplot.com/analysis/). In addition, we analyzed the expression of PRMT1 across brain regions through The Human Protein Atlas (https://www.proteinatlas.org/ENSG00000126457-PRMT1/brain). The expression of PRMT1 at both protein and RNA levels can be detected in all the brain regions analyzed and there doesn't seem to be region specificity for PRMT1 expression (Supplemental Figs. 1A–1B), suggesting that different locations in the brain may not cause the difference of PRMT1 expression across various brain tumor types. In line with this notion, a previous study reported a strong positive signal for PRMT1 protein as measured by immunohistochemical staining in over 75% of glioma tumor samples as compared to a weak signal in normal brain tissues [9]. Together, these data suggest that PRMT1 may play a role in the development of medulloblastoma.

We next asked if PRMT1 expression correlates with patient survival. To this end, we first analyzed the correlation between PRMT1 expression and SHH signaling, one of the predominant developmental pathways frequently activated in medulloblastoma, in particular, SHH subtype [2]. The SHH signaling score was calculated as geometric mean gene expression from SHH signaling (BioCarta-Online maps of metabolic and signaling pathway). We found that there is a significant anti-correlation between PRMT1 expression and SHH signature score by using medulloblastoma dataset GSE85212 (n = 763) (Fig. 1D). Then we performed survival analyses using 612 medulloblastoma samples from the Cavalli cohort (763 samples). We observed a significant correlation between high levels of PRMT1 mRNA expression with poor patient survival in SHH and Group 3 medulloblastoma patients (Fig. 1E and F), as well as a trend towards this correlation in Group 4 medulloblastoma patients, although not significant (Fig. 1G). But this correlation was not observed in WNT medulloblastoma patients (Fig. 1H).

3.2. *PRMT1 is important for medulloblastoma cell proliferation and survival*

The strong correlation between PRMT1 expression and poor survival of Group 3/Group 4/SHH medulloblastoma patients prompted us to examine the role of PRMT1 in medulloblastoma cell growth and survival. We chose to use the following two cell lines. DAOY is a classified SHH cell line carrying a mutation in TP53 whereas D283 is a long-established Group 3/Group 4 cell line with wild type TP53. Even though almost all Group 3 cell lines harbor *MYC* amplification, D283 has no *MYC* amplification but shows MYC overexpression at both mRNA and protein levels [10]. By using our previously validated inducible PRMT1 knockdown construct [4], we established inducible PRMT1 depletion in medulloblastoma cell culture. Upon addition of doxycycline (Dox), we confirmed efficient depletion of PRMT1 in DAOY cells, as shown by Western blot (Fig. 2A). PRMT1 knockdown markedly inhibited DAOY cell proliferation (Fig. 2B). To test whether PRMT1 promotes

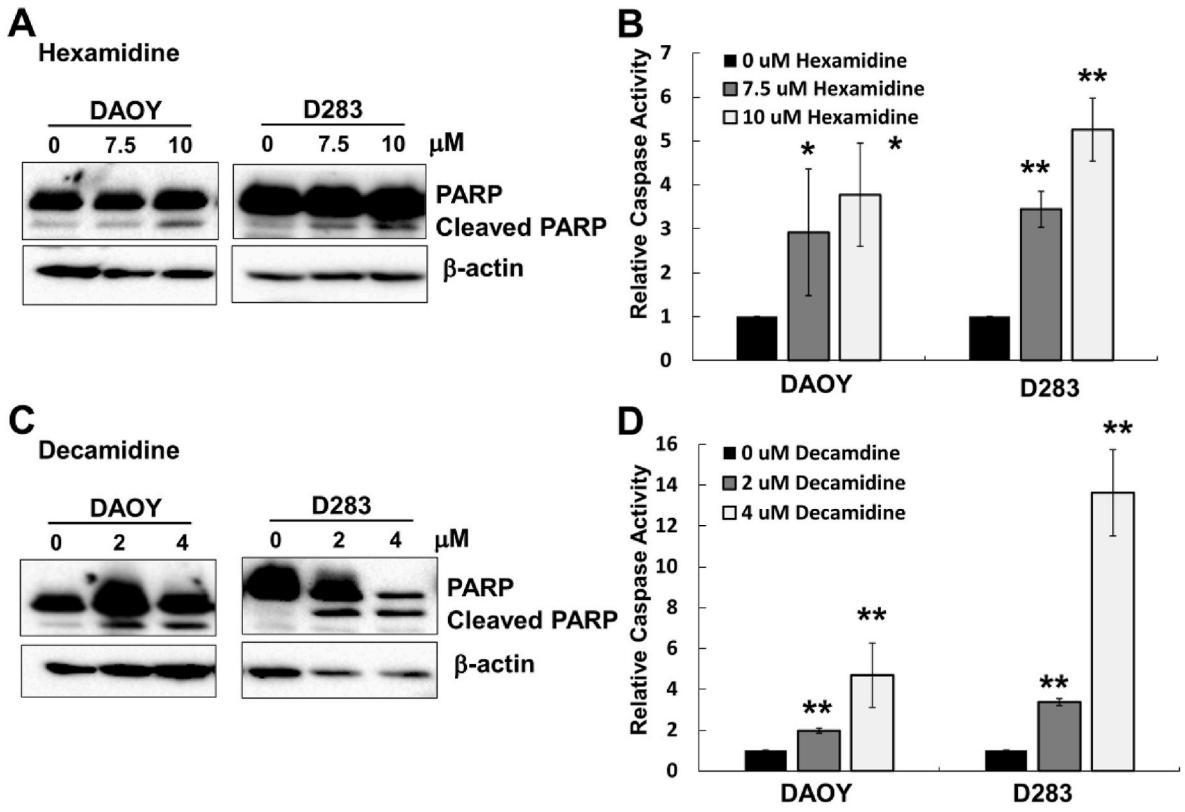

Fig. 4. Diamidine compounds induced cell apoptosis in human medulloblastoma cells. (A), Western blot showing the cleavage of PARP in human medulloblastoma cells treated with indicated concentrations of hexamidine for 24 h. **(B),** Caspase-3/7 activity assay of human medulloblastoma cells treated with indicated concentrations of hexamidine for 24 h. Data are mean ± SD (n = 3) relative to DMSO control. **(C),** Western blot showing the cleavage of PARP in human medulloblastoma cells treated with indicated concentrations of decamidine for 24 h. **(D),** Caspase-3/7 activity assay of human medulloblastoma cells treated with indicated concentrations of decamidine for 24 h. Data are mean ± SD (n = 3) relative to DMSO control. Student t-test. *: $P < 0.05$. **: $P < 0.01$.

medulloblastoma cell survival, we performed two independent assays to examine the effect of PRMT1 knockdown on cell apoptosis. First, as demonstrated by Western blot (Fig. 2A), PRMT1 attenuation induced cleavage of PARP in DAOY cells, indicating the activation of caspases and apoptosis. Second, PRMT1 depletion induced an increase of caspase-3/7 activity in DAOY cells (Fig. 2C). Notably, the critical role of PRMT1 in cell proliferation and survival was further confirmed in D283 cells (Fig. 2D–F). Together, these data demonstrate that PRMT1 plays an important role to promote medulloblastoma cell proliferation and survival, most likely to be independent of medulloblastoma subtypes.

3.3. *Dose-dependent efficacy of diamidine compounds of PRMT1 inhibitors in medulloblastoma cell culture*

Up to now, most small molecule PRMT inhibitors that have been developed are to target type I over type II PRMTs, but these compounds are not able to selectively target PRMT1 over other type I PRMTs [11]. The diamidine-related compounds were initially identified from focused library screening and these compounds have been validated for their specificity and selectivity towards inhibition of PRMT1 activity *in vitro* [12]. Our recent studies demonstrated a correlation between the cytotoxicity of these compounds in neuroblastoma cell culture with their inhibitory effects as determined by *in vitro* biochemical assays [4,13]. The rank order of these compounds in the cytotoxicity assay in different cancer cells was slightly different from that observed in the *in vitro* biochemical assay, suggesting that their potency may be context-different [12]. Importantly, we further verified the antitumor efficacy of potent diamidine compounds, furamidine and decamidine, in preclinical mouse models of neuroblastoma [4].

We next determined the efficacy of diamidine compounds in medulloblastoma cell culture. Our results demonstrated that all compounds we tested induced a dose-dependent growth inhibition at low micromolar concentrations in both DAOY and D283 cells (Fig. 3). Notably these compounds displayed a similar rank order of their cytotoxicity as we previously observed in neuroblastoma cells [4], with IC50 of 13.68 μM for furamidine, 3.23 μM for pentamidine, 3.71 μM for hexamidine, and 1.26 μM for decamidine in DAOY cells. Interestingly, we observed a slightly higher potency of these compounds in D283 cells as compared with DAOY cells. D283 cells are considered an intermediate group medulloblastoma cell line between Group 3 and 4, showing MYC overexpression [10]. A recent report identified PRMT5 as a critical regulator of MYC in MYC-driven (Group 3) medulloblastoma cells [3]. Consistently, D283 cells showed higher sensitivity to a PRMT5 inhibitor than DAOY cells [3]. Previous studies have demonstrated that diamidine-related compounds possess varying selectivity against PRMTs [10]. We reason that the slightly higher potency of diamidine compounds we observed in D283 cells may be due to combined inhibition of both PRMT1 and PRMT5. Furthermore, emerging evidence has provided a rational combinatorial inhibition strategy of type I PRMTs and PRMT5 to achieve synergistic killing in various cancer cell types [14–16]. The idea of simultaneous inhibition of PRMT1 and PRMT5 has not yet been tested in medulloblastoma, but we suppose that dual targeting of PRMT1 and PRMT5 may prove more efficacious than single agents and this notion is currently under active investigation.

As PRMT1 is considered as a ubiquitously expressed protein across human tissues [1], we next asked whether the potency of diamidine compounds we observed in medulloblastoma cells is due to their toxicity or specific inhibition of PRMT1. To this end, we isolated murine sympathetic neurons from superior cervical ganglia (SCG) of adult mice and examined the cytotoxicity of decamidine in SCG. We reason that if the

anti-proliferative efficacy of diamidine compounds is not due to their specific inhibition of PRMT1, then we would expect similar toxicity of SCG cells to these compounds as compared to medulloblastoma cells. As shown in the Supplemental Fig. 2, SCG exhibited resistance to decamidine and no dose-dependent suppression of cell viability was observed, suggesting that the anticancer effect of diamidine compounds in medulloblastoma cell culture is mainly due to PRMT1 inhibition.

3.4. Diamidine compounds induced medulloblastoma cell apoptosis

Lastly, we asked whether diamidine-related compounds induce medulloblastoma cell apoptosis. Indeed, in both DAOY and D283 cells, we observed a dose-dependent induction of apoptosis upon treatment with low micromolar concentrations of hexamidine (Fig. 4A and B) and decamidine (Fig. 4C and D), as demonstrated by an increase of cleaved PARP (Fig. 4A, C) as well as caspase 3/7 activity (Fig. 4B, D). This is in agreement with our previous observations of induction of neuroblastoma cell apoptosis by these compounds [4].

Notably, we observed a more dramatic increase of caspase 3/7 activity in D283 cells than DAOY cells upon treatment with decamidine (Fig. 4D). This finding is consistent with slightly higher potency of diamidine compounds in D283 cells as compared with DAOY cells (Fig. 3). Among all the diamidine-related compounds we tested, decamidine displayed the highest potency as demonstrated by suppression of cell viability (Fig. 3) as well as induction of cell apoptosis (Fig. 4). Compared with all the other compounds in this diamidine class, decamidine has been shown to exhibit the most potent effect against PRMT1, but slightly decrease selectivity against PRMT5 [12]. Given that PRMT5 has been shown in a recent study to be required for the survival of MYC-dependent medulloblastoma cells [3], simultaneous targeting of PRMT1 and PRMT5 by decamidine may bring the overall cellular arginine methylation below a certain threshold that is essential for cell survival, particularly in MYC-driven medulloblastoma cells, such as D283 cells. We propose two scenarios that can plausibly provide the molecular basis of this idea. First, PRMT1 and PRMT5 may share common substrates. Indeed, MYC has been shown to be arginine methylated by both PRMT1 and PRMT5, the activities of which may cooperate to regulate the stability and binding of MYC in glioblastoma [17]. It is plausible that MYC may also be regulated by both PRMT1 and PRMT5 in MYC-driven medulloblastoma cells. Second, PRMT1 and PRMT5 may function independently. This notion is supported by our observations as well as a recent report. Suppression of PRMT1 activity alone through either genetic (Fig. 2) or pharmacological (Figs. 3 and 4) approach, or a selective PRMT5 inhibitor [3] induced medulloblastoma cell apoptosis. Further studies are warranted to distinguish these two scenarios.

Given a variety of downstream substrates and targets, the functional complexity of PRMT1 is best reflected by their multiple roles in various cellular processes. Recent studies have implicated PRMT1 in cancer cell apoptosis, but its complex, and sometimes, opposite roles have been observed in different cancer types [18,19]. Our previous studies demonstrated an anti-apoptotic function of PRMT1 to promote neuroblastoma cell survival [4] whereas two other reports showed a pro-apoptotic activity of PRMT1 in lung and colon cancer cells [18,19]. In a mouse model of SHH medulloblastoma, an increased level of PRMT1 may promote apoptosis of neoplastic precursor cells [5]. These discrepancies may be due to different downstream substrates or targets of PRMT1 in distinct contexts. Nevertheless, our current study provides evidence supporting an essential function of PRMT1 in medulloblastoma cell proliferation and survival. We further showed anti-medulloblastoma efficacy of diamidine-related compounds at low micromolar concentrations. Notably, several diamidine compounds, such as furamidine, pentamidine, and hexamidine are FDA-approved drugs for treatment of other diseases, where the safety and efficacy of these compounds has been extensively assesses in a clinical setting [8]. Therefore, repurposing these FDA-approved reagents may provide a faster way of bringing new therapeutics for cancer treatment. Taken together, our findings suggest that targeting PRMT1 could be a viable therapeutic strategy for medulloblastoma.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbrep.2022.101364.

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