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REVIEW PAPER

Protein Arginine Methyltransferases from Regulatory Function to Clinical Implication in Central Nervous System

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Abstract

Arginine methylation, catalyzed by protein arginine methyltransferases (PRMTs), is a regulatory key mechanism involved in various cellular processes such as gene expression, RNA processing, DNA damage repair. Increasing evidence highlights the crucial role of PRMTs in human diseases, including cancer, cardiovascular and metabolic diseases. Here, this review focuses on the latest findings regarding PRMTs in the central nervous system (CNS), emphasizing their regulatory roles in neural stem cells, neurons, and glial cells. Additionally, we examine the connection between PRMTs dysregulation and neurological diseases affecting the CNS, including brain tumors, neurodegenerative diseases, and neurodevelopmental disorders. Therefore, this review aims to deepen our understanding of PRMTs-mediated arginine methylation in CNS and open avenues for developing novel therapeutic strategies for neurological diseases.

Graphical Abstract

PRMTs' role in neural cells and neurological diseases in CNS. PRMTs-mediated arginine methylation plays a significant role in multiple biological processes of neural cells via regulating protein–protein and protein-RNA interactions, such as NSC proliferation and differentiation, neuron morphogenesis and activity, glial cells development and function. Its dysregulation is closely linked to neurological diseases in CNS including brain tumors, neurodegenerative diseases, and neurodevelopmental disorders.

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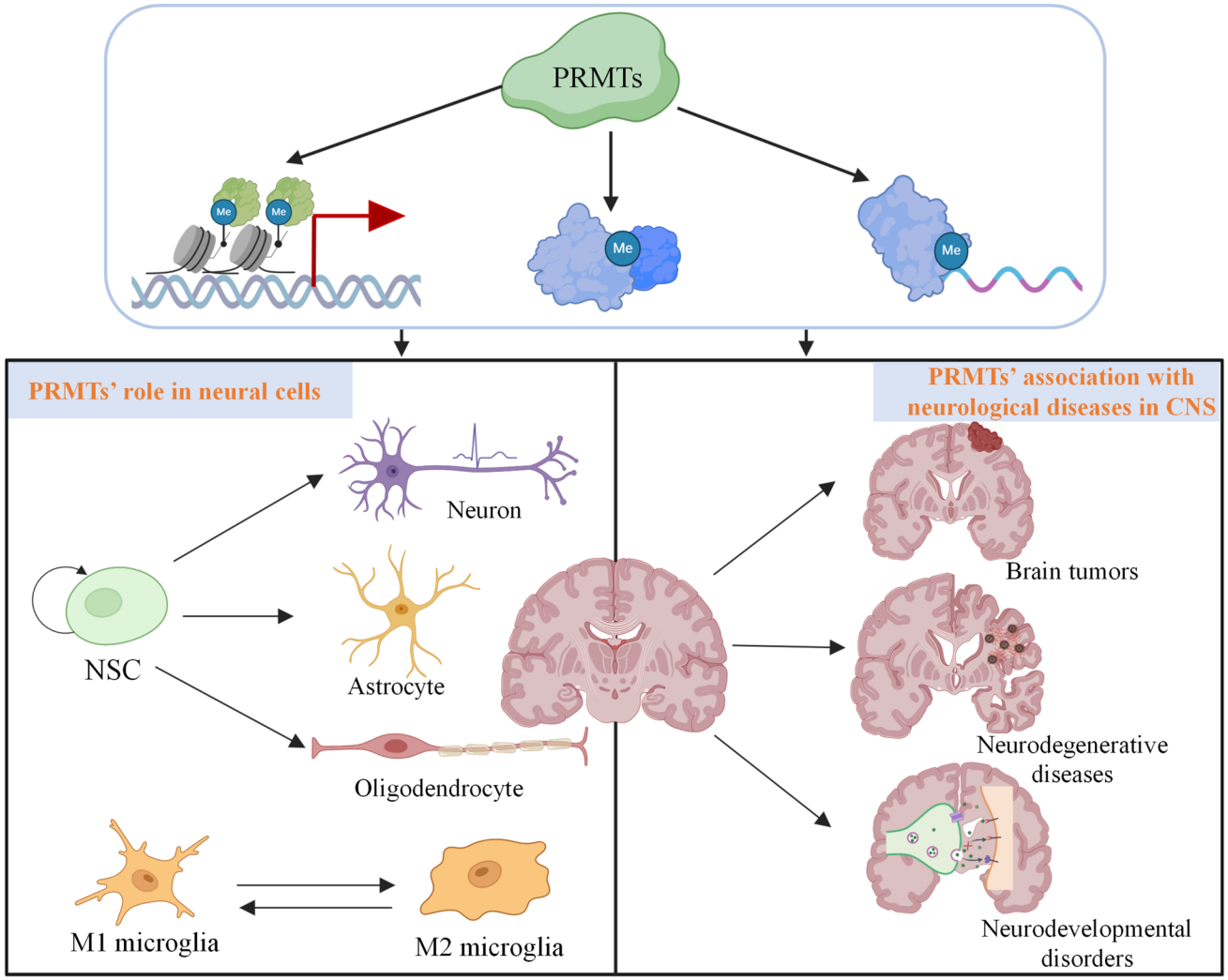

Keywords Arginine methylation · Protein arginine methyltransferases · Central nervous system · Neurological diseases

Introduction

Post-translational modifications (PTMs) add functional diversity to proteins by covalently attaching chemical groups after translation, altering their stability, localization, and interaction networks. Among the PTMs, arginine methylation, catalyzed by protein arginine methyltransferases (PRMTs), has gained significant attention. PRMTs transfer the methyl group from *S*-adenosyl-L-methionine (SAM) to the guanidino nitrogen atoms of arginine residue in proteins. This modification alters the hydrogen-bonding capacity of the guanidino group, thereby modulating protein–protein and protein-RNA interactions (Fuhrmann et al. 2015). In human cell lines, around 1 ~ 3.4% of arginine residues are methylated, which is as abundant as phosphorylation and ubiquitination (Zhang et al. 2021).

Like other modifications, arginine methylation recruits effector molecules, referred to as "readers", to newly created methyl-motifs (Gayatri and Bedford 2014; Wang and Bedford 2023). Tudor domain-containing proteins are the primary readers of methylarginine modifications (Gayatri and Bedford 2014; Wang and Bedford 2023). In humans, there are thirty-six Tudor domain-containing proteins; some of these proteins bind to methylarginine, while others interact with methyllysine motifs (Gayatri and Bedford 2014; Wang and Bedford 2023). For example, survival of motor neuron (SMN) engages with arginine-methylated RNA-binding proteins via its Tudor domain (Brahms et al. 2001; Friesen et al. 2001). Additionally, apart from Tudor domain-containing proteins, other domains and protein folds also demonstrate an affinity for methylated arginine residues (Wang and Bedford 2023).

The "erasers" for methylarginine still remains enigma. JmjC domain-containing protein 6 (JMJD6) is identified as the first enzyme proposed to catalyze arginine demethylation on histone substrates (Chang et al. 2007). However, the subsequent biochemical and structure evidence fails to confirm this catalytic activity, instead establishing it as a lysine hydroxylase (Webby et al. 2009; Cockman et al. 2022). Additionally, some members of JmjC domain-containing lysine demethylation (KDM), in purified form, are reported to possess arginine demethylation activity (Walport et al. 2016; Li et al. 2018; Bonnici et al. 2024). For example, isolated JmjC-KDM4 and KDM5 can catalyze demethylation of methylarginine of H2a, but this reaction may be altered by different substrate sequence contexts (Bonnici et al. 2024). However, further efforts need to focus on confirming their demethylation activity on methylarginine and demonstrating their biological relevance in cells.

The arginine methylation targets catalyzed by PRMTs include histones and non-histones, playing a key role in regulating gene expression, pre-mRNA splicing, RNA transport, DNA damage repair, and signal transducing (Blanc and Richard 2017; Wei et al. 2021). Increasing evidence has revealed that dysregulation of PRMTs activity is closely linked to disease pathogenesis. The therapeutic strategies targeting PRMTs have been effectively developed for various human diseases, particularly in cancer (Guccione and Richard 2019; Hwang et al. 2021; Wu et al. 2021). In this review, we will focus on the functions of PRMTs in neural cells and their relevance to diseases occurred in central nervous system.

The Enzymatic Activity of Protein Arginine Methyltransferases

There are three states of arginine methylation in cells (Fig. 1), including ω-N^G, N^G-asymmetric dimethylarginine (ADMA), ω-N^G, N^G-symmetric dimethylarginine (SDMA), and ω-N^G monomethylarginine (MMA). Therefore, PRMTs are accordingly classified into three types based on the final form of methylated arginine they produce. Type I PRMTs including PRMT1, 2, 3, 4 (also known as CARM1), 6, and 8 carry out the formation of ADMA. PRMT1 is responsible for the majority of ADMA production, accounting for 85% of total PRMTs activity in cells (Tang et al. 2000; Tewary et al. 2019). Additionally, PRMT8 harbors phospholipase activity, alongside its role as a methyltransferase. Type II PRMTs including PRMT5 and PRMT9 produce SDMA, of which PRMT5 plays a leading role in SDMA generation (Gillespie et al. 2024).

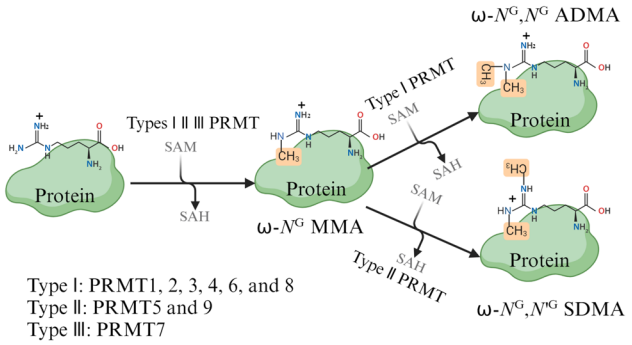

Fig. 1 PRMTs have arginine methyltransferase activity. There are three types of PRMTs catalyzing the formation of arginine methylation in protein by transferring the methyl group from SAM to the guanidino nitrogen atoms of arginine residue. Type I PRMTs including PRMT1, 2, 3, 4, 6, and 8 carry out the final formation of ADMA. Type II PRMTs including PRMT5 and PRMT9 are responsible for producing SDMA. Type III PRMTs only have PRMT7 and exclusively cause the formation of MMA

Type III PRMTs include only PRMT7, which exclusively causes the formation of MMA. Among these forms of arginine methylation, ADMA is the most abundant, while SDMA and MMA 10% and 1% of ADMA levels, respectively (Zhang et al. 2021).

Structurally, all PRMTs shares a core design that includes a N-terminal Rossman fold domain also referred to SAM-binding domain and a C-terminal β-barrel domain which mediates the formation of homo-dimerization required for active enzyme (Tewary et al. 2019). However, dimerization is not necessary for PRMT7 and PRMT9, because they possess two tandem Rossman fold domains due to gene duplication over evolutionary time, forming an intramolecular homodimer-like structure (Hasegawa et al. 2014; Yang et al. 2015).

Most of PRMTs are ubiquitously expressed in cells and are localized in both the cytoplasm and nucleus (Hwang et al. 2021). However, PRMT6 is predominantly found in the nucleus (Bouchard et al. 2018). In addition, PRMT8 is uniquely restricted to the brain and dwells in the plasm membrane (Lee et al. 2005).

Arginine and glycine repetitions of protein, namely RGG/RG motif, are the most favored methylated sites by PRMTs, while CARM1 preferentially modifies arginine residues locate within proline, glycine, and methioline (PGM) regions (Shishkova et al. 2017). PRMT7, on the other hand, targets arginine residues within RXR motifs, which are typically surrounded by lysine-rich amino acid sequences (Feng et al. 2013).

The Function of Arginine Methylation in Neural Cells

Conditional knockout of PRMT1 or PRMT5 in mice CNS led to the early death at postnatal 2 weeks, indicating the key roles of PRMTs-mediated arginine methylation on neural development (Bezzi et al. 2013; Hashimoto et al. 2016). Below, we summarize their expression (Table 1) and function in neural stem cells (NSCs), neuronal cells and glial cells (Fig. 2).

PRMTs and Neural Stem Cells

PRMTs and the Proliferation of Neural Stem Cells

PRMT1 was essential for NSCs proliferation and survival in mice (Hashimoto et al. 2022). PRMT1 deficiency activated cellular apoptotic pathway by increasing p53 protein level and upregulating p53-response pro-apoptotic genes, including *Pmaip1* and *Perp* (Hashimoto et al. 2022). Consequently, PRMT1-deficient mice NSCs displayed reduced proliferative capacity, forming smaller neurosphere compared to the control (Hashimoto et al. 2022).

Table 1 The expression of PRMT subtype in CNS cell types

PRMT Subtype	Expression in CNS cell types	Reference
PRMT1	Widely expressed in neurons, microglia, oligodendrocytes, and astrocytes	(Zhang et al. 2015; Hashimoto et al. 2021)
PRMT2	Expressed in the dendrites of neurons	(Hou et al. 2018)
PRMT3	Expressed in the cell bodies and dendrites of neurons	(Ikenaka et al. 2006; Miyata et al. 2010)
PRMT4	Expressed in post-synapses of neurons and astrocytes	(Selvi et al. 2015; Lim et al. 2017)
PRMT5	Expressed in neurons, astrocytes, and oligodendrocytes	(Huang et al. 2011; Calabretta et al. 2018)
PRMT6	Primarily expressed in neurons	(Damez-Werno et al. 2016; Bouchard et al. 2018)
PRMT7	Primarily expressed in neurons	(Lee et al. 2020)
PRMT8	Expressed in cell bodies and dendrites of neurons	(Kousaka et al. 2009; Lo et al. 2020)
PRMT9	Primarily expressed in neurons	(Shen et al. 2024)

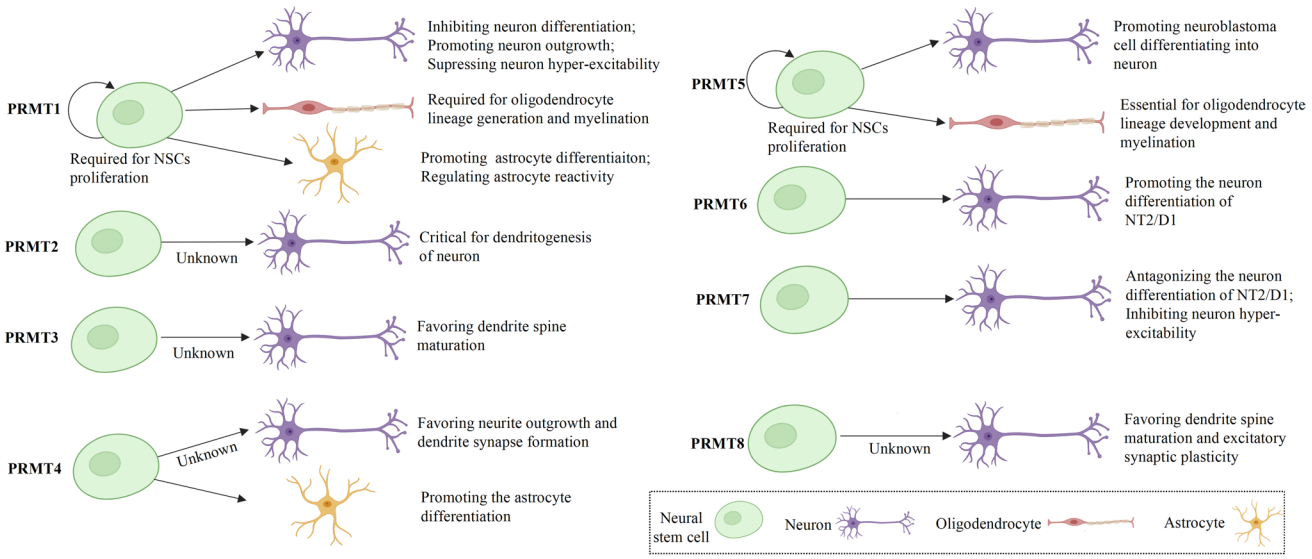

Fig. 2 PRMTs are involved in regulating physiological processes of neural cells. PRMTs play significant regulatory roles on the proliferation and differentiation of neural stem cell, neuron morphogenesis and activity, and the development and function of glial cells. Among them, PRMT1 and PRMT5 are well demonstrated to be essential for the proliferation and survival of NSC, and participate in NSC differentiation into neuron and oligodendrocyte. PRMT6 and PRMT7 are also found to participate in controlling neuron differentiation from NSCs. As the major enzyme for ADMA generation, PRMT1 is also involved in regulating physiological processes of neuron and glial cells, like neuron morphogenesis and excitability, astrocyte development and reactivity, as well as microgliosis. Other members of PRMTs including PRMT2, 3, 4, and 8 have great effects on neuron morphogenesis. Besides, PRMT4 is helpful for astrocyte development

PRMT5 also played a significant role in NSC viability. Knockout of PRMT5 in mouse NSCs led to abnormal splicing of many pre-mRNAs, including MDM4, a known inhibitor of p53 activity (Bezzi et al. 2013). This resulted in the activation of p53-mediated apoptotic signaling pathway, contributing to NSCs death (Bezzi et al. 2013). Consequently, these knockout mice showed reduced brain size and early postnatal lethality (Bezzi et al. 2013). Additionally, PRMT5 was involved in regulating NSCs proliferation acting as a regulator of gene expression via histone modification. PRMT5 interacted with Schwann cell factor 1 (SC1, also known as PRDM4) to comprise an epigenetic regulatory complex that directs symmetric dimethylation of H4 at R3 (H4R3me2s) (Chittka et al. 2012). Overexpressing of mycSC1 delayed the time of neurogenesis from NSCs in mice cerebral cortex while this phenomenon was absent in mice expressing a mutant form of mycSC1 that could not recruit PRMT5 (Chittka et al. 2012).

PRMTs and the Differentiation of Neural Stem Cells

CNS-specific PRMT1 deficiency led to postnatal growth retardation in mice, with most dying within 2 weeks of birth (Hashimoto et al. 2016). This may be attributed to perturbations of the oligodendrocyte lineage generation from NSCs and severe hypomyelination of mature oligodendrocytes (Hashimoto et al. 2016). On a molecular level, PRMT1 deletion resulted in the decreased expression of several key transcriptional factors essential for oligodendrocyte specification and mature, including *Olig1*, *Olig2*, *Nkx2.2* and *Sox10*, indicating the requirement of PRMT1 for NSCs differentiation into oligodendrocyte (Hashimoto et al. 2016). Signal transducer and activator of transcription 3 (STAT3) is the critical transcriptional factor to induce astrocyte from NSCs by promoting the expression of glial fibrillary acidic protein (GFAP), the astrocytic marker gene (Nakashima et al. 1999). PRMT1 enhanced the activity of STAT3 transcriptional activation on astrocytic genes expression through arginine methylation (Honda et al. 2017). Knockdown of PRMT1 in mice NSCs suppressed *Gfap* expression, impairing astrocyte differentiation from NSCs (Honda et al. 2017). Additionally, PRMT1 downregulation induced the neuronal-like differentiation by reducing the stemness of NSCs (Chen et al. 2021). The epigenetic factors EZH2, LSD1 and HDAC1 are accepted to be required for preserving neural stemness (Hsieh et al. 2004; Han et al. 2014a, b; Lei et al. 2019). PRMT1 interacted with deubiquitinase USP7 to coordinate ribosome and proteasome activity, maintaining their expression in mice NSCs (Chen et al. 2021). Therefore, when PRMT1 was depleted in NSCs, the protein level of EZH2, LSD1 and HDAC1 was decreased, promoting the cells to differentiate into neuron (Chen et al. 2021).

PRMT4 controlled astrocyte differentiating from NSCs via depositing asymmetric demethylation to R17 of H3 (H3R17me2a), an active histone mark (Selvi et al. 2015). This mark enhanced *Nanog*-modulated miR17-92 activity, favoring astroglial fate commitment in embryoid bodies (EBs) derived from human embryonic stem cells (Selvi et al. 2015). Therefore, the inhibition of PRMT4 activity led to the abnormal forming of astrocytes both in human cells and the animal model zebrafish (Selvi et al. 2015).

The ratio of PRMT5 short isoform, resulting from exon skipping, to the full isoform was changed when LA-N-5 human neuroblastoma cells differentiated into neurons induced by 13-*cis*-retinoic acid (Sohail et al. 2015). This result implied PRMT5 might play a role in neuronal differentiation from NSCs, however, the precise function required further investigation.

PRMT6 interacted with subunits of Polycomb repressive complex 1and 2 ((PRC1 and PRC2) to facilitate the deposition of repressive histone mark trimethylation of H3 at lysine 27 (H3K27me3) on rostral *HOXA* genes (*HOXA1-5*), which are transcriptionally activated during neuronal differentiation of human neural progenitor cells (NPCs) NT2/D1 cell line induced by during all-*tans* retinoic acid (ATRA) (Stein et al. 2016). While the occupancy of PRMT6 and the resulting asymmetric dimethylation of H3 at R2 (H3R2me2a) on these genes loci was successively lost during ATRA-induced differentiation, favoring the neurogenesis from NT2/D1 (Stein et al. 2016). This result indicated that PRMT6 may be involved in NSCs differentiating to neuron cells by controlling the expression of neuron differentiation-associated genes.

MLL4 was required for retinoic acid (RA)-induced differentiation of NT2/D1 stem cells by activating the expression of differentiating genes including *HOXA1-3* and *NESTIN* through trimethylation of H3 at K4 (H3K4m3) modification (Dhar et al. 2012). However, PRMT7-mediated H4R3me2s antagonized the binding of MLL4 on these genes, thereby inhibiting the neuronal differentiation of NT2/D1 induced by RA (Dhar et al. 2012). Moreover, as an epigenetic modifier, PRMT7 can be involved in NPC proliferation and differentiation by regulating the expression of cell cycle and neuronal function-related genes, such as *CDKN2A* and *SYP*, via H4R3me2s modification (Shen et al. 2025). It is found that PRMT7 depletion inhibited the expansion of NPC population but promoted their differentiating into neurons (Shen et al. 2025).

PRMTs and Neuronal Cells

PRMTs and the Neuronal Morphogenesis

Downregulation of PRMT1 in mouse Neuro2a cells inhibited neurite outgrowth under serum deprivation, indicating

the role of PRMT1 on neuronal morphogenesis (Miyata et al. 2008). In rat hippocampal neurons, axon outgrowth and dendrite complexity decreased when PRMT1 activity was inhibited (Amano et al. 2020). PRMT1 was also involved in the Golgi organization which is critical for axon and dendrite outgrowth (Amano et al. 2020). It was found that PRMT1 can methylate C-terminal domain of SCY1 like pseudokinase 1 (SCYL1), a significant player in Golgi morphology, and this modification was necessary for its interaction with the subunit of coat protein complex I (COPI) γ_2-COP to facilitate Golgi organization (Amano et al. 2020).

PRMT2 is essential for dendritogenesis of neuron (Hou et al. 2018). The actin nucleator Cordon-bleu (Colb) plays a pivotal role on dendrites and dendritic branch formation (Ahuja et al. 2007). PRMT2 acted as a binding partner of Colb and catalyzed its C-terminal domain methylation to promote the association of Cobl with actin, which was helpful for dendritic arbor formation (Hou et al. 2018). Therefore, overexpression of PRMT2 in hippocampal neurons isolated from mice increased the number of dendrites and dendritic branch-points, while PRMT2 knockdown contributed to the opposite effects (Hou et al. 2018).

PRMT3 regulated the stability of ribosome protein S2 (rpS2), which affected ribosome maturation (Miyata et al. 2010). This interactions of PRMT3 and rpS2 cooperatively supported the local translation of α subunit of the calcium/calmodulin-dependent protein kinase II (αCaMKII) in response to neurotrophic factor activation in dendrite (Miyata et al. 2010). Hence, PRMT3 downregulation in rat hippocampus neuron led to the failure of increased αCaMKII abundance upon BDNF stimulation, and consequently decreased spine area (Miyata et al. 2010).

PRMT4 was enriched in the post-synaptic density (PSD) of post-synaptic membrane and co-localized with post-synaptic marker PSD 95 in rat hippocampal neurons (Lim and Alkon 2017). The genetic or pharmacological inhibition of PRMT4 contributed to a dramatically raised in the cluster size of key post-synaptic proteins including PSD95 and *N*-methyl-D-aspartate receptor subunit 2B (NR2B) in synapses, in accompany with the enhanced complexity of dendritic structure (Lim and Alkon 2017). These results indicated the regulatory role of PRMT4 in dendrite morphology and synapse formation possibly via arginine-methyl modifications of PSD proteins. Additionally, PRMT4 can be involved in neuritogenesis by methylation of a RNA-binding protein HuD, a critical factor for neuron differentiation via binding mRNAs containing the AU-rich elements to preserve them from degradation (Fujiwara et al. 2006). PRMT4-mediated HuD methylation was unfavorable for its interaction with $p21^{cip/waf1}$ mRNA, resulting in decreased stability of $p21^{cip/waf1}$ mRNA (Fujiwara et al. 2006). Therefore, PC12 cells with PRMT4 depletion harbored increased $p21^{cip/waf1}$ protein abundance, leading to cell cycle arrest and accelerated neurite outgrowth in response to the stimulation of nerve growth factor (Fujiwara et al. 2006).

PRMT8, primarily localized at the neuronal synapse, is involved in the dendrite spine maturation (Lee et al. 2017; Lo et al. 2020; Guan et al. 2021). PRMT8-mediated methylarginine of dendritic RNA-binding protein G3BP1 suppressed Rac1-PAK1 signaling, controlling synaptic actin dynamics (Lo et al. 2020). Mice cortical neurons with PRMT8 depletion exhibited decreased turnover of F-actin and defect morphology of dendritic spines with a higher number of filopodia and shaft synapses (Lo et al. 2020). Additionally, PRMT8 regulated the dendrite morphogenesis of mice Purkinje cells dependent on its phospholipase activity (Guan et al. 2021). Mice with PRMT8 knockout displayed abnormal motor behaviors as well as the abnormal dendritic arborization and altered cerebellar structure (Guan et al. 2021). Upon PRMT8 deletion, the increased phosphatidylcholine and decreased hydrolyzed products including choline and phosphatidic acid were observed, highlighting the deficiency of PRMT8-mediated phosphatidylcholine hydrolysis may contribute to this phenotype (Guan et al. 2021).

PRMT9 plays a critical role in neuronal morphogenesis and activity, particularly in synapse development and function (Shen et al. 2024). PRMT9 regulated RNA splicing by methylating SF3B2, a key splicing factor, influencing the inclusion or skipping of exons in genes involved in synaptic function such as *Grin1* (Shen et al. 2024). Therefore, PRMT9 knockout in hippocampal neurons led to abnormal synaptic morphology, including reduced spine density and size (Shen et al. 2024).

PRMTs and the Neuronal Activity

PRMT1 is accepted as a regulator in neuronal excitability through modulating the activity of KCNQ2 potassium channel (Kim et al. 2016). PRMT1 catalyzed the arginine methylation of KCNQ2 to promote its interaction with phosphatidylinositol-4,5-bisphosphate (PIP2) which is required for this channel activity (Kim et al. 2016). Thus, hippocampal neurons in *Prmt1*-heterozygous mice exhibited a reduced KCNQ2 channel activity and increased neuronal hyper-excitability (Kim et al. 2016).

In *C. elegans*., PRMT5 mediated sensory and motor neuron responses to the environment stimuli by methylating G protein-coupled receptor (GPCR) DOP-3, a D2-like dopamine receptor homologous to the human D2 dopamine receptor, which plays a critical role in chemosensory and locomotor behavior (Likhite et al. 2015). The worms expressing mutant PRMT5 displayed the hypersensitivity to dilute octanol and a defect basal slowing when they encountered the food (Likhite et al. 2015). Moreover, PRMT5 can methylate another GPCR, the SER-2 tyramine receptor, which shares a conserved arginine methylation motif with

its human counterpart, to regulate *C. elegans* locomotion (Bowitch et al. 2018). The regulatory role of PRMT5 in *C. elegans* neurons implied that it might be also involved in modulating neuronal function in humans.

NALCN is a key player in establishing the resting membrane potential (RMP) in neurons. PRMT7 inhibited NALCN activity by catalyzing its methylation, thereby reducing neuron excitability (Lee et al. 2019). Therefore, hippocampal dentate granule cells lacking PRMT7 in mice displayed hyper-excitability with the depolarization of RMP, decreased threshold currents, and increased excitability (Lee et al. 2019). PRMT7 also modulated the expression of Shank3 which is a scaffolding protein of HCN channel proteins to control the number of HCN channel in mice hippocampal CA1 neurons (Lee et al. 2020). When PRMT7 function was defect in mice, CA1 neurons showed a higher polarized resting potential and input resistance (Lee et al. 2020).

PRMT8 also plays a crucial role in the neuronal function. PRMT8 deficiency caused a significant reduction of NMDA receptor subunit GluN2A in mice hippocampus, resulting in the decreased GluN2A-mediated currents (Penney et al. 2017). Electrophysiological recordings from these PRMT8-deficient mice showed defects in excitatory synaptic function and plasticity (Penney et al. 2017).

PRMTs and Glial Cells

PRMT1 plays a critical role in the development and function of glial cells. Most mice with conditional deletion of PRMT1 in brain died at postnatal 2 weeks (Hashimoto et al. 2016). In these mice, the number of oligodendrocyte progenitor cells (OPCs), premyelinating oligodendrocytes and the mature oligodendrocytes were dramatically reduced. Besides, the mature oligodendrocytes were severely hypomyelination (Hashimoto et al. 2016). Moreover, mice with microglia PRMT1 deficiency showed the failure of remyelination upon cuprizone diet-induced demyelination, characterized by the prolonged microgliosis, astrogliosis, and decreased accumulation of OPCs during remyelination phase (Lee et al. 2022a, b). PRMT1 deletion led to the reduced active histone mark acetylation of H3 at lysine 27 (H3K27ac) deposition in the promoter of major histocompatibility complex (MHC)-associated genes, impairing their transcriptional programs (Lee et al. 2022a, b). This ultimately led to the loss of MHC-associated microglia required for efficient remyelination (Lee et al. 2022a, b). PRMT1 was also involved in postnatal microgliosis and astrogliosis in mice (Hashimoto et al. 2021a, b). Mice with PRMT1 knockout showed significantly heightened astrocytes and microglia reactivity at postnatal 8 days (Hashimoto et al. 2021a, b).

Inhibitors of differentiation or DNA binding 2 (Id2) and Id4 are known to be the repressors of oligodendrocyte differentiation (Kondo and Raff 2000; Wegner 2007). As an epigenetic regulator, PRMT5-mediated H4R3me2a modification suppressed their expression via increasing the DNA methylation on their CpG regions (Huang et al. 2011). In the rat OPCs with downregulation of PRMT5, increased expression of Id2 and Id4 perturbed oligodendrocyte maturation (Huang et al. 2011). Additionally, PRMT5 can inhibit acetylation of neighboring lysine residue of histone via H4R3me2s deposition, affecting the expression of many genes critical for oligodendrocyte development (Scaglione et al. 2018). In PRMT5-deficient OPCs, the oligodendrocyte signature genes were significantly downregulated, whereas genes involved in p53 signaling pathway were upregulated, leading to a significant reduction of mature oligodendrocytes as well a severe hypo-myelination (Scaglione et al. 2018). In addition, PRMT5 can methylate platelet-derived growth factor receptor (PDGFRα) which plays a critical role in OPCs proliferation, migration, and commitment of oligodendrocytes (Calabretta et al. 2018). This methylarginine reduced the affinity of Cbl E3 ligase to PDGFRα, preserving PDGFRα from degradation (Calabretta et al. 2018). As a result, mice lacking PRMT5 showed decreased PDGFRα level at the plasma membrane, resulting in fewer mature oligodendrocytes, dysmyelination, and death at 3 weeks after birth (Calabretta et al. 2018).

The links of arginine methylation to neurological diseases.

PRMTs and Primary Brain Tumors

Medulloblastoma (MB) and glioblastoma (GBM) are the most common malignant primary brain tumors in the CNS, representing the leading cause of cancer-related death in children and young adults, respectively (Ostrom et al. 2022). PRMTs are frequently upregulated in GBM, and patients with elevated PRMT levels often experience poor outcome (Samuel et al. 2021). Below, we mainly discussed the pathogenic mechanisms that PRMTs contribute to GBM and MB, along with their potential as therapeutic targets for these tumors (Table 2).

PRMTs and Glioblastoma

In glioma, PRMT1 was upregulated in tumor cells and associated with poor outcome of the patients (Wang et al. 2012; Dong et al. 2018). Downregulation of PRMT1 in glioma cell lines caused decreased proliferation and increased apoptosis, and the nude mouse xenografts with PRMT1 depletion showed the reduced tumor growth (Wang et al. 2012). A recent study found that PRMT1 expression and its associated histone modification H4R3me2a were reduced in IDH1 mutant gliomas, impairing the transcriptional activation of PTX3, a key factor in inflammation and autophagy

Table 2 The association of PRMTs with neurological diseases occurred in CNS

Types of neurological diseases	Members	Targets	Function	Reference
Primary brain tumors				
Glioblastoma (GBM)	PRMT1	H4R3	Advantageous for the proliferation and survival of tumor cell	Wang et al. 2012
	PRMT2	H3R8	Promoting GBM stem-like cell (GSC) proliferation and growth	Dong et al. 2018
	PRMT3	HIF1α	Helpful for tumor cell growth and progression	Liao et al. 2022
	PRMT5	Proliferation-associated genes	Promoting tumor cell growth	Braun et al. 2017
		hnRNPA1	Favoring the therapeutic resistance of mTOR therapy	Holmes et al. 2019
	PRMT6	RCC1	Helpful for GSC proliferation and growth	Huang et al. 2021
	PRMT8	Unknown	Its expression was reduced and associated with favorable outcome of patients, while the truncated isoform was helpful for the proliferation of tumor cells	Simandi et al. 2015; Hernandez and Dominko 2016
Medulloblastoma (MB)	PRMT1	BAD	Upregulated in neoplastic precursor cells and promoting apoptosis	Sakamaki et al. 2011
		MYC	Helpful for the survival of MB cell line	Gu et al. 2022
	PRMT5	MYC	Involved in MYC-amplified Group 3 MB and beneficial for cell survival	Chaturvedi et al. 2019
Neurodegenerative diseases				
ALS/FTD	PRMT1	FUS	Modulating FUS subcellular localization and aggregates	Dormann et al. 2012; Scaramuzzino et al. 2013; Suarez-Calvet et al. 2016; Tradewell et al. 2012; Yamaguchi and Kitajo 2012
	PRMT8	FUS	Modulating FUS aggregates	Scaramuzzino et al. 2013
		CREB1	Acting as a protective role for spinal cord motor neurons	Simandi et al. 2018
AD	PRMT4	NOS	Regulating NO production and cerebral blood flow	Clemons et al. 2022
	PRMT5	E2F-1	Inhibiting E2F-1-activated apoptotic signaling and reducing Aβ-induced toxicity	Quan et al. 2015
PD	PRMT1	AIF	Promoting the nuclear translocation of AIF and activating PARP1-mediated cell apoptosis	Nho et al. 2020
HD and polyQ diseases	PRMT4	HTT	Beneficial for HTT solubility and providing protection for neuron survival	Ratovitski et al. 2022
	PRMT5	H2AR3 and H4R3	Restoring aberrant gene expression and RNA processing	Ratovitski et al. 2015
	PRMT6	HTT	Required for HTT axon transportation and neuron viability	Ratovitski et al. 2022; Migazzi et al. 2021
		mutant AR	Enhancing the transactivation of mutant AR	Scaramuzzino et al. 2015
MS	PRMT1	H4R3	Promoting IL-17 expression and Th17-induced EAE	Sen et al. 2018a, b

Table 2 (continued)

Types of neurological diseases	Members	Targets	Function	Reference
	PRMT4	H3R17	Activating IL-17 expression and Th17-induced EAE	Sen et al. 2018a, b
	PRMT5	SREBP1	Promoting transcriptional programs of Th17 differentiation by enhancing SREBP1 stability and transcriptional activity	Webb et al. 2020
		Sm, Snrp A1, and hnRNPK	Favoring the normal splicing of Trpm4, and consequently helpful for IL-2 production	Sengupta et al. 2021
Neurodevelopmental disorders				
Rett syndrome	PRMT1	MeCP2	Inhibiting the heterochromatin accumulation of MeCP2	Schmidt et al. 2022
	PRMT6	MeCP2	Inhibiting the heterochromatin accumulation of MeCP2	Schmidt et al. 2022
Fragile X syndrome	PRMT1	FMRP	Leading to abnormal function of FMRP	Stetler et al. 2006; Blackwell et al. 2010
Intellectual disability	PRMT7	Unknown	Patients with PRMT7 mutation underwent intellectual disability	Akawi et al. 2015; Kernohan et al. 2016; Agolini et al. 2018
Epilepsy	PRMT1	KCNQ2	Promoting KCNQ2 activity	Kim et al. 2016
	PRMT7	Unknown	Patients with PRMT7 mutation underwent epilepsy	Akawi et al. 2015; Kernohan et al. 2016; Agolini et al. 2018
SCZ	PRMT7	Unknown	Acting as a risk gene of SCZ	Fiorica and Wheeler 2019

regulation (Lathoria et al. 2023). This deficiency in PRMT1-mediated activation led to increased ferritinophagic and autophagic flux, possibly accounting for the better prognosis of glioma patients with IDH1 mutant (Lathoria et al. 2023). Therefore, targeting this PRMT1-PTX3 axis could provide therapeutic opportunities, particularly in enhancing the sensitivity of glioma cells to ferroptosis inducers (Lathoria et al. 2023).

PRMT2 activated oncogenic transcriptional program via asymmetric dimethylation of H3 at R8 (H3R8m2a) modification in GBM (Dong et al. 2018). Depletion of PRMT2 in GBM cell lines suppressed several oncogenic signaling pathways, including PI3K-AKT, MAPK, JAK-STAT and Wnt/β-catenin pathways, were strikingly repressed upon (Dong et al. 2018). Therefore, these cells showed decreased cell growth, GBM stem-like cell (GSC) self-renewal, and reduced tumor growth (Dong et al. 2018).

PRMT3 expression was upregulated in GBM patients and negatively associated with their outcome (Liao et al. 2022). PRMT3 promoted the expression and stability of HIF1α, as the key regulator of glycolysis pathway in GBM (Liao et al. 2022). Consequently, GBM cells with PRMT3 downregulation or inhibition showed impaired glycolytic metabolism, leading to reduced tumor growth and progression (Liao et al. 2022).

In GBM, PRMT5 can regulate the splicing of proliferation-associated genes to support the survival of tumor cells (Braun et al. 2017). PRMT5 knockdown caused the intron retention in genes involved in regulating cell cycle and DNA replication, resulting in their decreased expression in GBM cells (Braun et al. 2017). As a result, these cells suffered from cell cycle arrest, cell senescence and apoptosis (Braun et al. 2017). PRMT5 was also involved in therapeutic resistance to mechanistic target of rapamycin (mTOR) inhibition in GBM (Holmes et al. 2019). The activation of salvage pathway stimulating internal ribosome entry site (IRES)-mediated protein synthesis is the major cause of the resistance to mTOR therapy (Martin et al. 2011). The methylation activity of PRMT5 was increased responding to mTOR inhibition (Holmes et al. 2019). This promoted the methylation of hnRNPA1 and facilitated its binding to the internal IRES of mRNAs, thus supporting protein synthesis under mTOR inhibition (Holmes et al. 2019). Multiple studies have showed that PRMT5 expression was positively associated with growth of GBM tumor cells and negatively correlated with patient outcomes, making it a promising therapeutic target of GBM (Han et al. 2014a, b; Yan et al. 2014; Banasavadi-Siddegowda et al. 2017; Braun et al. 2017). Nowadays, clinical trials have been underway using PRMT5 inhibitors in GBM patients, with GSK3326595 showing efficacy in several tumor types including GBM, in a phase I study (Banasavadi-Siddegowda et al. 2018; Siu et al. 2019).

In glioma, PRMT6 displayed a positive association with glioma grade and adverse prognosis of patients (Huang et al. 2021). Casein kinase 2 (CK2) catalyzed the phosphorylation of PRMT6, impeding its ubiquitination and enhancing its

stability in GBM (Huang et al. 2021). High levels of PRMT6 promoted the methylation of regulator of chromatin condensation 1 (RCC1) at R214, favoring its association with chromatin and activation of RAN-GTP which is beneficial for cell proliferation (Huang et al. 2021). Consequently, PRMT6 upregulation enhanced the mitotic activity of tumor cells (Huang et al. 2021).

PRMT8′s role in glioma is less well defined, but some evidence suggests it may act as a tumor suppressor. In mESCs-derived neural cells, PRMT8 depletion led to changes in gene expression patterns linked to gliomagenesis (Simandi et al. 2015). Additionally, the expression of PRMT8 was identified to be decreased following the glioma development and associated with favorable outcome of GBM patients, suggesting a suppressor role in GBM (Dong et al. 2018). However, a truncated PRMT8 isoform was shown to be required for the proliferation of GBM cells (Hernandez and Dominko 2016).These findings indicate the involvement of PRMT8 in glioma, but its precise function and mechanism require further exploration.

PRMTs and Medulloblastoma

Transformation of cerebellar granule cell precursors (GCPs) due to Sonic hedgehog (Shh) pathway activation can lead to the development of a specific subgroup of MB known as Shh-type, which accounts for approximately 30% of MB cases (Northcott et al. 2019). In *Patched1* heterozygous mice, a Shh-type MB model, the deletion of *Btg1* identified as a negative regulator of GCPs proliferation did not cause the increased cell proliferation as well as tumor frequency (Ceccarelli et al. 2020). Interestingly, PRMT1 was found to be upregulated in the neoplastic GCPs of these mice (Ceccarelli et al. 2020). PRMT1 can activate apoptosis pathway by arginine methylation of pro-apoptotic factor Bcl-2 antagonist of cell death (BAD), preventing the Akt-mediated BAD phosphorylation and promoting its mitochondrial translocation (Sakamaki et al. 2011). This PRMT1-mediated apoptosis may counterbalance the effects of *Btg1* loss on. However, contrary findings were observed in human MB cells, where shRNA-mediated downregulation or diamidine-induced inhibition of PRMT1 increased the apoptosis (Gu et al. 2022). These conflicting results suggest that PRMT1 is involved in regulating the survival of MB cells, but the discrepancy between the mouse model and human study likely reflects differences in genetic context. Further investigation is need to be performed in consideration of PRMT1 as the drug target of MB.

In MYC-amplified Group 3 MB, genetic downregulation or pharmacological inhibition of PRMT5 caused the decreased MYC protein abundance, leading to increased apoptosis (Chaturvedi et al. 2019). PRMT5 catalyzed arginine methylation in MYC, which was beneficial for MYC stability (Chaturvedi et al. 2019). This interaction of PRMT5 and MYC has been previously described in GBM, where PRMT5 contributed to the activation of MYC target genes through depositing H4R3me2s as an epigenetic modifier (Mongiardi et al. 2015). Additionally, PRMT5 acted as a key regulator of another member of MYC family MYCN protein which is a major driver of neuroblastomas (NBs), a solid tumor arising in the sympathetic nervous system (Park et al. 2015). PRMT5-mediated arginine methylation also enhanced MYCN stability, thereby promoting the survival of the NBs cell lines (Park et al. 2015). Collectively, these findings suggest that PRMT5 may be an attractive therapeutic target for tumors driven by the members of MYC family in the nervous system.

PRMTs and Neurodegenerative Diseases

Neurodegenerative diseases are characterized by the progressive loss of neurons in the central or peripheral nervous system, affecting millions of people worldwide (Wilson et al. 2023). PRMTs-mediated arginine methylation is implicated in several pathological processes associated with neurodegenerative diseases, including protein aggregation, synaptic and neuronal network dysfunction, and inflammation. Below, we discussed the involvement of PRMTs in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and other polyglutamine (polyQ) diseases, and Multiple sclerosis (MS) (Table 2).

PRMTs and Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD)

In ALS and FTD, nuclear import defects and cytoplasmic aggregation of Fused in sarcoma (FUS) are the key pathological mechanisms. Arginine methylation plays a crucial role in regulating FUS subcellular localization and aggregation (Dormann et al. 2012; Scaramuzzino et al. 2013; Hofweber et al. 2018; Qamar et al. 2018; Ryan et al. 2018). FUS nuclear import is mediated by Transportin TRN which binds to the proline-tyrosine nuclear localization signal (PY-NLS) of FUS (Dormann et al. 2012). There are three RGG domains, the preferential methylation sites of PRMTs, preceding PY-NLS (Dormann et al. 2012). The arginine methylation in these RGG domains disrupted the interaction of Transportin with PY-NLS, thereby affecting the nuclear localization of FUS (Dormann et al. 2012). Additionally, the RGG/RG motifs in FUS C-terminal domain are crucial for FUS phase separation (Suarez-Calvet et al. 2016; Hofweber et al. 2018; Qamar et al. 2018). Arginine methylation in these motifs reduced FUS-mediated phase separation and stress granule (SG) formation, while un- or mono-arginine-methylation of FUS was helpful for the formation of FUS

inclusions as seen in FTD-FUS patients but not ALS-FUS patients (Suarez-Calvet et al. 2016; Hofweber et al. 2018; Qamar et al. 2018).

The concentrations of PRMT1 and ADMA were upregulated in the cerebrospinal fluid of ALS patients compared to the controls (Ikenaka et al. 2019). Accordingly, the high ratio of ADMA/L-arginine was associated with the progression and poor outcome of ALS (Ikenaka et al. 2019). Actually, PRMT1-mediated arginine methylation of FUS has been linked to its subcellular localization and aggregates in ALS/FTD (Dormann et al. 2012; Tradewell et al. 2012; Yamaguchi and Kitajo 2012; Scaramuzzino et al. 2013; Suarez-Calvet et al. 2016). PRMT1 downregulation reduced the cytoplasmic localization of FUS mutants, suggesting that PRMT1-mediated arginine methylation may contribute to toxic gain-of-function in FUS mutants (Dormann et al. 2012; Tradewell et al. 2012). Furthermore, genetic or pharmacologic inactivation of PRMT1 was observed to cause FUS methylation state from ADMA to un-methylation or MMA FUS state, enhancing FUS binding affinity with the nuclear import receptor transportin-1 and promoting its cytoplasmic protein aggregation with transportin-1 (Suarez-Calvet et al. 2016).

PRMT8 may play a protective role for spinal cord motor neuron (MNs), whose progressive loss is a typical pathological feature of ALS. Like PRMT1, PRMT8 co-localized with FUS (Scaramuzzino et al. 2013). Pharmacologic inhibition of PRMT8 resulted in both nuclear and cytosolic accumulation of FUS wild-type and ALS-linked FUS mutants in MNs (Scaramuzzino et al. 2013). Additionally, PRMT8 expression was gradually increased compared to other PRMTs members and had a relative enrichment in MNs over other spinal cord cell types during MNs differentiation (Simandi et al. 2018). The spinal cord MNs with PRMT8 deficiency underwent seriously neurodegenerative-related phenotypes, such as neuron muscle junction (NMJ) fragmentation, impaired axonal transport and premature accumulation of aging pigments (Simandi et al. 2018). In these MNs, deletion or inhibition of PRMT8 caused accumulation of unrepaired DNA double-strand breaks and decreased cAMP response-element-binding protein 1 (CREB1) expression level, disrupting the cAMP-mediated neuron-protection transcriptional network (Simandi et al. 2018).

PRMTs and Alzheimer's Disease (AD)

In addition to amyloid-β (Aβ) plaques and tau neurofibrillary tangles, dysregulation of nitric oxide (NO) signaling which results in the derangement of cerebral blood flow (CBF) contributes to the pathogenesis of AD (Hansra et al. 2019). ADMA, a non-canonic ligand of nitric oxide synthase (NOS), caused NOS uncoupling and inhibited its function (Choi et al. 2020). In the aged female 3xTg-AD mice, which exhibit tau and Aβ pathologies, the levels of PRMT4 in the hippocampus compared to controls were found to be elevated (Clemons et al. 2022). This PRMT4 overexpression correlated with NOS uncoupling, reduced NO production and increased oxidative stress via peroxynitrite, ultimately resulting in impaired CBF. Pharmacologic inhibition of PRMT4 using TP-064 was shown to reverse these effects, improving NOS function, NO metabolite production, and restoring CBF (Clemons et al. 2022). This finding suggests that targeting PRMT4 may offer therapeutic strategies for improving vascular function in AD (Clemons et al. 2022).

On the contrary, PRMT5 expression was decreased in hippocampus tissue of AD patients (Quan et al. 2015). Similar PRMT5 downregulation was observed in mice primary cortical neurons and human SH-SY5Y cells both treated by Aβ peptide (Quan et al. 2015). When PRMT5 was knockdown in SH-SY5Y cells with overexpression of human Aβ precursor protein, these cells had an increased apoptosis (Quan et al. 2015). Additionally, PRMT5 depletion caused exacerbated Aβ-induced paralysis in a transgenic Caenorhabditis elegans strain CL2006, the worm model of AD (Quan et al. 2015).

PRMTs and Parkinson's Disease (PD)

PRMT1 was found to be upregulated in human dopaminergic neuronal cell line treated by 1-Methyl4-phenylpyridinium iodide (MPP^+), a toxic metabolite of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to selectively kill dopaminergic neurons in substantia nigra to induce symptom of PD in animal models (Nho et al. 2020). Under this condition, nuclear translocation of apoptosis-inducing factor (AIF) was enhanced, promoting Poly (ADP-ribose) polymerase-1 (PARP1)-mediated apoptosis (Nho et al. 2020). However, when PRMT1 was downregulated, this apoptotic activity was inhibited, attenuating MPP^+-induced cell death (Nho et al. 2020). Additionally, in PRMT1 haploinsufficient mice treated with MPTP, neuronal death in substantia nigra was reduced and motor symptoms were less severe (Nho et al. 2020).

PRMTs and Huntington's Disease (HD) and Other PolyQ Diseases

Huntingtin (HTT) has been shown to stimulate PRMT5 activity toward histone modification, while mutant HTT impaired PRMT5-mediated SDMA of substrates like H2A, H4 and Cajal body marker coilin (Ratovitski et al. 2015). This disruption in PRMT5-mediated SDMA activity may partially explain the aberrant gene expression and RNA processing in HD (Ratovitski et al. 2015). Therefore, restoration of PRMT5 function either by overexpressing the PRMT5/MEP50 complexes or deleting H4R3me2s demethylase

JMJD6 attenuated the toxic effects of mutant HTT in mouse primary cortical neurons (Ratovitski et al. 2015).

HTT protein itself harbors multiple arginine methylation sites, which is advantageous for HTT solubility (Ratovitski et al. 2022). Alterations of arginine methylation at specific sites were detected in HD patient-derived immortalized striatal precursor cells (ISPNs) lines compared to the normal (Ratovitski et al. 2022). PRMT4/CARM1 and PRMT6 were identified as the major enzymes responsible for HTT methylation (Ratovitski et al. 2022). Overexpression of PRMT4 or PRMT6 in HD ISPNs protected neurons from stress induced by deprivation of growth factor (Ratovitski et al. 2022). Additionally, PRMT6-mediated arginine methylation at R118 of HTT was required for HTT axonal transportation (Migazzi et al. 2021). PRMT6 downregulation in mice striatal and cortical cells expressing mutant HTT disrupted trafficking of HTT and caused neuronal death, while PRMT6 overexpression restored HTT axonal transport and neuronal viability (Migazzi et al. 2021). In HD fly model, PRMT6 overexpression also restored axonal and neuromuscular junction defects to normal level (Migazzi et al. 2021).

In contrast, PRMT6 had an antagonistic role in spinal and bulbar muscular atrophy (SBMA), a polyQ diseases ascribing to polyglutamine expansion of androgen receptor (AR) (Scaramuzzino et al. 2015). PRMT6 enhanced the toxicity of mutant AR in SBMA by promoting its transactivation through arginine methylation (Scaramuzzino et al. 2015). Therefore, downregulation of PRMT6 Drosophila ortholog DART8 suppressed polyglutamine-expanded AR-induced neurodegenerative phenotypes in SBMA fly model (Scaramuzzino et al. 2015).

PRMTs and Multiple Sclerosis (MS)

MS is a chronic inflammatory neurodegenerative disease of CNS, characterized by demyelinating lesions in the brain and spinal cord due to the infiltration of immune cells, including T cells and B cells, into CNS (Filippi et al. 2018). Immune system dysregulation, like the increased Th1 and Th17 inflammatory responses, deficient Th2 and regulatory T cell responses, is currently known cause for MS (Webb et al. 2017; Filippi et al. 2018). The roles of PRMTs on T cell function associated with MS has been explored.

PRMT1 has been identified as a potential therapeutic target for Th17-mediated MS (Sen et al. 2018a, b). PRMT1 promoted the expression of IL-17 expression by depositing H4R3me2a modification on IL-17 promoter, facilitating the stimulatory STAT3 binding and blocking the inhibitory STAT5 binding (Sen et al. 2018a, b). Downregulation or pharmacological inhibition of PRMT1 in mouse naïve T cells severely impaired the generation of IL-17$^+$ cells (Sen et al. 2018a, b). Consequently, inhibiting PRMT1 activity alleviated Th17-induced experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. (Sen et al. 2018a, b).

PRMT4, working in concert with steroid receptor coactivator 1 (SRC1), also promoted Th17 differentiation (Sen et al. 2018a, b). Phosphorylation of SRC1 by protein kinase C theta (PKC-θ), a key signaling T cell receptor (TCR) molecule, recruited PRMT4 to the IL-17 promoter locus to deposit the active histone mark H3R17me2a while preventing the repressive histone mark H3K9me3, thereby, enhancing the IL-17 transcriptional program (Sen et al. 2018a, b). Hence, SRC1 deletion led to reduced IL-17 + T cells, inflammation, and MS development in EAE model (Sen et al. 2018a, b).

PRMT5 is implicated in MS pathogenesis by its regulation of memory CD4$^+$ Th cell responses to antigen stimulation (Webb et al. 2017, 2020; Sengupta et al. 2021). PRMT5 was essential for the reactivation of memory CD4$^+$ Th cells by affecting the secretion of IL-2, an important pro-proliferative T cell cytokine (Webb et al. 2017). As a result, PRMT5-specific inhibitor impaired the proliferation and expansion of resting memory Th1 and Th2 CD4$^+$ T cells under the inducing condition, consequently, suppressing T cell response and inflammation in EAE model (Webb et al. 2017). Additionally, the regulatory role of PRMT5 on alternative splicing (AS) may be responsible for the association of PRMT5 with CD4$^+$ Th cell proliferation (Sengupta et al. 2021). PRMT5 knockout led to the 20th exon loss of transient receptor potential melastatin 4 (Trpm4), a Ca^{2+} activated Na^+ channel regulating T cell cytokine production, which would undergo nonsense-mediated decay due to the production of out-of-frame shift (Sengupta et al. 2021). The decreased Trpm4 protein level attenuated the translocation of nuclear factor of activated T cells (NFAT) into the nuclear, suppressing IL-2 transcription, and consequently leading to reduced T cell growth and proliferation (Sengupta et al. 2021). PRMT5 was also associated with MS by modulating Th17 differentiation (Webb et al. 2020). In T cells, PRMT5 methylated the cholesterol biosynthesis regulator SREBP1, promoting the activity of retinoid-related orphan receptor gamma (RORγt), a critical transcriptional factor controlling Th17 signature genes expression (Webb et al. 2020). Loss of PRMT5 in the CD4$^+$ Th cell reduced Th17 differentiation and pathogenic Th17 in response to myelin oligodendrocyte glycoprotein (MOG), protecting mice from developing EAE (Webb et al. 2020).

PRMTs and Neurodevelopmental Disorders

Neurodevelopmental disorders are a class of diseases that affect brain development and function, harming the health of about three percent children worldwide. Although numerous genes associated with neurodevelopmental disorders have been identified, functional studies suggest that these genes

are often linked to common pathways, like synaptic signaling, transcriptional or epigenetic regulation, and protein synthesis. Increasing evidence indicates that PRMTs play a significant role in brain cell development and function through acting as transcriptional regulators or epigenetic factors. Below, we explored the role of PRMTs in intellectual disability, epilepsy, and schizophrenia (SCZ) (Table 2).

PRMTs and Intellectual Disability

The regulation of PRMTs-mediated arginine methylation on the function of several factors associated with intellectual disability has been investigated, such as methyl CpG binding protein 2 (MeCP2). In Rett syndrome, a type of intellectual disability disorder, methylation at multiple arginine sites of MeCP2 affected its role in chromatin organization (Schmidt et al. 2022). The accumulation of MeCP2 on the heterochromatin was drastically inhibited when R92, R162 and R167 of MeCP2 were methylated (Schmidt et al. 2022). Additionally, methylation at the commonly mutated R106 site in Rett syndrome was identified (Schmidt et al. 2022). R106 mutants was found to reduce DNA binding and heterochromatin clustering, indicating this methylation may be involved in regulating the interaction of MeCP2 with chromatin (Schmidt et al. 2022). Of PRMTs, PRMT1 or PRMT6 are likely responsible for these modifications of MeCP2, and their upregulation disrupted MeCP2-mediated heterochromatin organization (Schmidt et al. 2022).

Fragile X Mental Retardation Protein (FMRP) is a significant mRNA-translational regulator in the brain (Brown et al. 2001). Loss-of-function of FMRP is the known cause of Fragile X syndrome, characterized by intellectual disability, learning and memory impairments (Prieto et al. 2019). Arginine methylation was detected in the RGG domain of FMRP, and PRMT1 may be responsible for this modification (Stetler et al. 2006; Blackwell et al. 2010). (Stetler et al. 2006; Blackwell et al. 2010). Among these modified sites, methylation at R533 and R538, or R543 and R545 particularly enhanced the binding of FMRP with G-quadruplex mRNA and polyribosome (Blackwell et al. 2010).

The methyltransferase activity of PRMT7 is also indispensable for intellectual development. Mutations in PRMT7 were linked to intellectual disability syndrome (Akawi et al. 2015; Kernohan et al. 2016; Agolini et al. 2018; Cali et al. 2023). Of these mutations, homozygous deletion at the transcription start site of PRMT7 or a homozygous nonsense mutation contributed to severe intellectual disability, likely due to reduced arginine methylation in the core histones H2B and H4 (Kernohan et al. 2016; Agolini et al. 2018). These mutations may alter the expression of genes critical for intellectual development, leading to the observed disability phenotype.

PRMTs and Epilepsy

Mutations in KCNQ potassium channel, a key determinant of neuronal excitability, are associated with epilepsy (Maljevic et al. 2010). PRMT1-catalyzed arginine methylation of KCNQ2 facilitated the interaction of KCNQ2 with PIP2, enhancing the channel activity (Kim et al. 2016). Hence, mice with *Prmt1*-heterozygous displayed neuronal hyperexcitability and epileptic seizures (Kim et al. 2016).

PRMT7 is also implicated in epilepsy. Individual with PRMT7 null mutation underwent symptomatic generalized epilepsy along with severe intellectual disability, and was treated with anti-epilepsy drugs valproic acid and levetiracetam at age 4 (Kernohan et al. 2016). Other patients harboring PRMT7 mutations also had epileptic seizures (Akawi et al. 2015; Agolini et al. 2018).

PRMTs and Schizophrenia

Transcriptome-wide association study suggest PRMT7 as a risk gene of SCZ (Fiorica and Wheeler 2019). A recent study demonstrated that PRMT7 is the target gene of SCZ risk SNPs at 16q22.1 (Shen et al. 2025). In monolayer cell and cerebral organoids models, PRMT7 downregulation led to reduced NPCs proliferation and increased neuronal differentiation (Shen et al. 2025). The dysregulation of PRMT7 on NPCs' function may contribute to SCZ pathogenesis (Shen et al. 2025).

Biological Models for Studying the Function of PRMTs in the Central Nervous System

Monolayer cell lines and transgenic mice are primarily used models for exploring the roles of PRMTs in neural cells and neurological diseases. These models have revealed that PRMTs were crucial for neural stem cell self-renewal and differentiation (Bezzi et al. 2013; Chen et al. 2021; Hashimoto et al. 2022; Shen et al. 2025), neuronal morphogenesis and function (Miyata et al. 2010; Lee et al. 2017; Hou et al. 2018; Shen et al. 2024), and glial cell lineage specification during neurodevelopment (Selvi et al. 2015; Hashimoto et al. 2016; Calabretta et al. 2018). Their association with neurological diseases pathogenesis also has been demonstrated in these models (Tradewell et al. 2012; Scaramuzzino et al. 2015; Banasavadi-Siddegowda et al. 2017; Dong et al. 2018; Sen et al. 2018a, b; Simandi et al. 2018; Ceccarelli et al. 2020; Webb et al. 2020; Huang et al. 2021; Liao et al. 2022; Ratovitski et al. 2022). However, both model systems exhibit limitations. For instance, monolayer cell lines fail to recapitulate the ordered interactions among heterogeneous neural cell populations, potentially obscuring mechanistic insights. Murine models are valuable to simulate how neurological disorders progress, while they may not fully

recapitulate the complexity of the human brain due to the difference in genetic background and brain architecture. For example, human neural progenitor cells display greater diversity and longer cell cycles compared to mice (Haldipur et al. 2019; Liu et al. 2023). Additionally, murine cerebellar development lacks radial glial progenitor cells, which is a human-specific cell type critical for higher cognitive functions such as memory and language (Haldipur et al. 2019).

In recent years, three-dimensional (3D) human brain organoids derived from induced pluripotent stem cells (iPSCs) have emerged as a transformative platform for studying human brain development and neurological diseases. These self-organizing structures mimic the cellular diversity and spatial organization of the early human brain, offering a more physiologically relevant system than monolayer cell lines and animal models (Lancaster et al. 2013; Bose et al. 2021). Transcriptomic analyses showed that brain organoids cultured for 250–300 days exhibited developmental trajectories analogous to the perinatal human brain (Gordon et al. 2021). Long-term cultured organoids develop spontaneously active neural networks, with action potentials that can be abolished by neurotransmitter receptor antagonists (Ghatak et al. 2021).

Brain organoids are increasingly employed to investigate neuropathological mechanisms and screen therapeutic candidates (Mariani et al. 2015; Qian et al. 2016; Meng et al. 2020; Szebényi et al. 2021; Zhao et al. 2021; Liu et al. 2022; Notaras et al. 2022; Li et al. 2023; Zhang et al. 2023; Shen et al. 2025). By employing 3D brain organoid models, PRMT7 is well established as a risk of gene of SCZ by regulating NPC proliferation and differentiation (Shen et al. 2025). Further research can apply brain organoids to model PRMTs-related neurological diseases and test clinical interventions.

PRMT Inhibitors in Therapeutic Development: Current Landscape and Clinical Perspectives

PRMTs have emerged as promising therapeutic targets, particularly in oncology. Among the PRMTs family, inhibitors against PRMT1 and PRMT5 dominate current drug development pipelines, with over 30 candidates under investigation, half of which are in clinical trials. The most advanced candidate, GSK3326595, represents the sole PRMT5 inhibitor progressing through Phase II trials in myeloid neoplasms (Watts et al. 2024). The detailed information of PRMTs inhibitors clinical trials has been recently reviewed and summarized in REF (Li et al. 2019; Wu et al. 2021).

Recent advances highlight brain-penetrant PRMT5 inhibitors as potential therapies for CNS malignancies. PRT811, a selective PRMT5 inhibitor, shows high brain penetrance and can effectively inhibit cell growth in a panel of patient-derived xenograft models of GBM in ex vivo 3D cultures (Zhang et al. 2020). PRT811 has entered Phase I trials for advanced solid tumors, CNS lymphomas, and gliomas (Zhang et al. 2020). JBI-778 is another brain-penetrant PRMT5 inhibitor and is poised for clinical evaluation in brain tumors (Sivanandhan et al. 2023). JBI-778 exhibited highly efficacious in orthotopic glioma models, particularly in the treatment of patients with spliceosome mutations (Sivanandhan et al. 2023). Another PRMT5 inhibitor LLY-283 is also demonstrated to effectively cross blood–brain barrier, disrupting aberrant splicing of transcriptome including cell cycle genes (Sachamitr et al. 2021). LLY-283 suppressed the growth of GBM stem cells and prolonged the survival of mice with orthotopic patient-derived xenografts (Sachamitr et al. 2021).

These findings emphasize the translational potential of PRMT5 inhibition in recalcitrant CNS cancers, while challenges remain. Early trials targeting mTOR in GBM yielded limited success, partly due to adaptive PRMT5 upregulation (Holmes et al. 2019). This highlights the need for combinatorial strategies or next-generation inhibitors to address resistance mechanisms. Furthermore, the development of isoform-selective PRMT inhibitors and rigorous biomarker-driven studies will be critical to optimizing therapeutic efficacy and minimizing off-target effects.

Conclusions and Future Perspective

As a common PTM like phosphorylation and ubiquitination, arginine methylation has gathered increasing attention. Through modulating protein–protein and protein-RNA interactions, PRMTs-mediated arginine methylation plays the critical roles in a range of biological processes in neural cells, and their dysregulation are associated with neurological diseases.

PRMTs have clearly been implicated in the proliferation and differentiation of NSCs, neurogenesis and neuron function, and the development of oligodendrocyte lineages. However, their roles in microglia and astrocyte remain largely unexplored. Microglia, the primary innate immune cell of brain, are key player in brain development, homeostasis, and diseases (Li and Barres 2017; Butovsky and Weiner 2018). Astrocytes, the most abundant glia cell type in CNS, are closely associated with both physiological and pathological processes of the CNS (Lee et al. 2022a, b). The two kinds of cells exhibit strong heterogeneity and plasticity in response to the environmental stimulation, which is relevant to health and diseases (Butovsky and Weiner 2018; Lee et al. 2022a, b). A recent study revealed that PRMT1-mediated arginine methylation is essential for remyelination following cuprizone (CPZ) diet-induced demyelination in mice through controlling the transition of phagocytic microglia into MHC-associated microglia, suggesting the involvement

of PRMTs in modulating the generation and activation of different microglia population (Lee et al. 2022a, b). Therefore, further investigation into the roles of PRMTs in microgliosis and astrogliosis, both in normal and disease contexts, is warranted.

Currently, research has primarily focused on exploring the role of PRMTs in brain tumors. PRMT5 has been identified as a valuable therapy target for GBM, with small molecular drugs specifically inhibiting the activity of PRMT5 already undergoing clinical trial. However, there are significant gaps in our understanding of the links between PRMTs and neurodevelopment disorders. PRMT7 is the only member of PRMT family that display a direct association with neurodevelopment disorders, where its mutations lead to intellectual disability and seizures (Akawi et al. 2015; Kernohan et al. 2016; Agolini et al. 2018). Additionally, PRMT7 has been suggested as the risk gene of SCZ (Fiorica and Wheeler 2019; Shen et al. 2025). Actually, a line of evidence has implied that PRMTs might be linked to neurodevelopment disorders. Defects in the myelination are reported to be associated with autism (Deoni et al. 2014; Hardan et al. 2016). Both PRMT1 and PRMT5 are essential for oligodendrocyte maturation and myelination, whose defects have been well-known to be associated with ASD (Hashimoto et al. 2016; Scaglione et al. 2018). Conditional deficiency of PRMT1 or PRMT5 in mouse brain led to serious hypomyelination, indicating that dysregulation of these PRMTs may be involved in ASD. However, the relevance of PRMTs with neurodevelopment disorders urgently needs to be extensively elucidated.

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Declarations

Conflict of interests The authors declare no competing interests.

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