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Protein Arginine Methyltransferases in Cardiovascular and Neuronal Function

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Abstract

The methylation of arginine residues by protein arginine methyltransferases (PRMTs) is a type of post-translational modification which is important for numerous cellular processes, including mRNA splicing, DNA repair, signal transduction, protein interaction, and transport. PRMTs have been extensively associated with various pathologies, including cancer, inflammation, and immunity response. However, the role of PRMTs has not been well described in vascular and neurological function. Aberrant expression of PRMTs can alter its metabolic products, asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA). Increased ADMA levels are recognized as an independent risk factor for cardiovascular disease and mortality. Recent studies have provided considerable advances in the development of small-molecule inhibitors of PRMTs to study their function under normal and pathological states. In this review, we aim to elucidate the particular roles of PRMTs in vascular and neuronal function as a potential target for cardiovascular and neurological diseases.

Keywords

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INTRODUCTION

Arginine is a basic α-amino acid that is involved in numerous biological processes [1]. The synthesis of urea and creatine utilize arginine for nitrogen balance and muscle metabolic demands [2]. As a free amino acid, arginine is a precursor for the formation of nitric oxide and glutamate, which are important neurotransmitters that can modulate vessel tonicity and nerve conductance [2]. As a residue on histones and other proteins, arginine can be methylated to regulate DNA transcription and post-translational modifications, affecting a variety of cellular processes (e.g. signal transduction, DNA repair, and mRNA alterations) [3,4].

The methylation of arginine is catalyzed by protein arginine methyltransferases (PRMTs) to form ω-N^G-monomethylated arginine (MMA), ω-N^G, N^G-asymmetric dimethylarginine (ADMA), and ω-N^G ,N'^G-symmetric dimethylarginine (SDMA) [5]. There are 11 different PRMT enzymes, categorized into 3 subtypes in accordance with their site of methylation [3]. Type I (PRMT1, PRMT2, PRMT3, PRMT4, PRMT6, PRMT8) PRMT enzymes are responsible for the formation of MMA as an intermediate before the formation of their end-product ADMA. Type II (PRMT5, PRMT9) PRMT enzymes also catalyze the formation of MMA as an intermediate before the formation of their end-product SDMA [6]. PRMT7 is a type III enzyme responsible for monomethylation of the arginyl residue to form MMA [3]. Although PRMT10 and PRMT11 were predicted to display type II PRMT activity, they have not been well characterized in their activity and physiological function, and thus have not been formally classified within these subcategories [7].

The post-translational modification of histones, in addition to DNA methylation, can influence gene expression [8] and regulation through arginine methylation by activation (H4R3me2a, H3R2me2s, H3R17me2a, H3R26me2a) or repressive (H3R2me2a, H3R8me2a, H3R8me2s, H4R3me2s) histone markers [6]. Proteins can also act as substrates to modulate various processes including DNA repair, transcription, receptor trafficking, and protein stability [9,10]. Interestingly, there are numerous arginine-methylated proteins that have been identified in the heart [11], such as two sites of arginine methylation on cardiac sodium channels associated with mutations causing channelopathies (i.e. Brugada and long QT type 3 syndromes) [12]. In the brain, arginine-methylated proteins have been associated with synaptic transmission and were identified as membrane G protein receptors, ion channels, and vesicular-bounded proteins [13]. Additionally, arginine- and glycine-rich motifs are among the most active sequences for PRMTs to mediate protein-protein interactions and nucleic acid to bind to downstream targets [6], which can activate or repress gene and protein function for potential drug targets to treat neurological and cardiovascular disorders. Currently, most of the literature describes the role of PRMTs in the development and prognosis of cancer pathologies. However, this review will discuss PRMTs in the context of underexplored areas of basic science and biomedicine particularly involving cardiac, cardiovascular and neurological disorders.

The role of PRMT and ADMA in cardiovascular disease

Increased PRMT activity can result in enhanced metabolic products such as ADMA and MMA, both linked to an increased risk for cardiovascular disease based on their propensity

to inhibit nitric oxide synthase (NOS) [5]. Accumulation of the endogenous NOS inhibitor, ADMA, an L-arginine analog, significantly reduced the synthesis of the potent vasodilator NO and contributes to cardiovascular disease pathogenesis [14–18]. Additionally, clearance of ADMA occurs through the proteolysis of arginine methylated proteins, releasing free methylarginines, (*i.e.*, ADMA) metabolized to L-citrulline and dimethylamine by dimethylarginine dimethylaminohydrolase (DDAH) [19,20]. Methylarginines (*e.g.* ADMA, SDMA, and MMA) can also be metabolized in mitochondria via a deamination reaction by alanine-glyoxylate aminotransferase 2 (AGXT2) to generate α-keto-δ-(N^G,N^G-dimethylguanidino) valeric acid. However, as a secondary pathway for the clearance of ADMA, AGXT2 can utilize ADMA, SDMA, and MMA as a substrate. Findings from Rodionov *et al.* indicate that overexpression of human AGXT2 in mice resulted in a reduction of ADMA levels in plasma and liver [21,22], whereas AGXT2-deficient mice displayed an increase in ADMA plasma and brain, heart, and liver tissue to develop hypertension [23]. However, some ADMA (~10%) can escape degradation via DDAH or AGXT2, and exit the cell via cationic amino acid transporters, which can also mediate the uptake of ADMA from plasma or neighboring cells [24]. Although small amounts of free ADMA in the plasma can be cleared via urinary excretion (~20%), the primary mechanism for the breakdown of ADMA occurs through DDAH (~80%) [24–26]. The proposed mechanism involves the overabundance of ADMA, which in turn, inhibits NOS, thereby reducing NO bioavailability to cause endothelial dysfunction. Indeed, improper balance between PRMTs and DDAH can lead to abnormal levels of nitric oxide that can cause various cardiovascular and neurodegenerative pathologies, including atherosclerosis, hyperglycemia, Alzheimer's, Parkinson's disease, and excitotoxicity after stroke [27–30].

DDAH exists as two isoforms in the cytoplasm. DDAH-1 is associated with tissues expressing neuronal NOS (nNOS), including the brain, pancreas, skeletal muscle, heart, liver, and kidneys [31], while DDAH-2 is localized in tissues expressing endothelial NOS (eNOS) [14]. DDAH-1 is thought to be responsible for metabolizing more than 70% of ADMA residues [16]. However, the clearance of ADMA via DDAH is compromised in patients with high cardiovascular risk factors, including hypercholesterolemia, hypertension, stroke, coronary artery disease, and myocardial infarction [32–34]. These risk factors are associated with a decrease in DDAH expression/activity to cause an increase in circulating levels of ADMA. Furthermore, dysregulation in PRMT or DDAH function could enhance ADMA levels. Indeed, PRMT1 expression was enhanced and DDAH-2 was reduced in coronary heart disease patients [35]. Therefore, potential treatments for cardiovascular disease could focus on stabilizing PRMT and DDAH function to reduce the accumulation of ADMA and other arginine-methylated proteins, thereby reducing the risk of cardiovascular disease.

The accumulation of ADMA via arginine methylation has not been well understood in the context of cardiac pathology. Onwuli *et al.* identified 58 non-histone arginine-methylated proteins in cardiac tissue, which indicates that arginine methylation in cardiomyocytes is relevant in cardiac function [11]. Furthermore, Onwuli *et al.* also reported that in a model of cardiac cell hypertrophy, H9c2 cells had a significant increase in size accompanied by a reduction in arginine methylation [11]. The same group also investigated specific cardiac troponin arginine methylation in human hearts [36]. Troponins binds to calcium to mediate

interactions between actin and myosin, regulating muscle contraction. Mutations at the cardiac troponin binding and inhibitory subunits are associated with sudden cardiac death, heart failure, hypertrophic, and dilated cardiomyopathies [36]. The study from Onwuli *et al.* suggests that arginine methylation can occur in various arginine sites (R74, R79, R146, R148) of the inhibitory subunit of cardiac troponin. Although no specific function has been discovered, the methylation of these arginine sites in the inhibitory subunit of cardiac troponin was reduced in hypertrophic cardiomyopathy as compared to dilated cardiomyopathy, which suggests there is a relevant function for arginine methylation in the progression of different cardiomyopathies [36]. Additionally, the study from Tang *et. al.* demonstrates that the accumulation of arginine-methylated metabolites in chronic heart failure was associated with diastolic dysfunction [37]. Among the arginine methylated derivatives, ADMA was the strongest predictor for disease progression and long-term adverse outcomes, which indicates that arginine methylation and ADMA clearance both play an important role in cardiovascular health.

The methylation of arginine could also affect cardiac and neuronal electrophysiology, more specifically via the post-translational modification of ion channels [12,38]. Cardiac ion channels are responsible for initiating and conducting signals to modulate depolarization and repolarization during action potentials [39]. Mutations in cardiac ion channels have been associated with several pathologies, which include cardiac arrhythmias, long QT syndrome type 3, and Brugada syndrome [39,40]. For instance, a mutation in sodium channel (*i.e.*, $Na_V1.5$) at R526 or R680 is sufficient to cause cardiac channelopathies, which include Brugada syndrome, and sudden infant death syndrome, respectively. Additionally, $Na_V1.5$ is important for the initiation of the fast sodium current during cardiac action potentials and can also be post-translationally modified via phosphorylation or arginine methylation. For instance, Beltran-Alvarez *et. al.* demonstrated that PRMT3 and PRMT5 can methylate the voltage-gated sodium channel 1.5 ($Na_V1.5$) *in vitro* to increase its cell surface expression [41]. Although these preliminary findings suggest that PRMTs could play a relevant role in cardiac function, further studies are still necessary to understand the specific role of arginine methylation in channelopathies and vascular disease.

The potential therapeutic role of PRMTs in circulation under pathological conditions (*e.g.*, cerebral ischemia) also remains unclear. Nevertheless, studies have shown that ADMA plays an essential role in the modulation of cerebral blood flow [42]. ADMA causes endothelium-dependent vasoconstriction to increase arterial stiffness and decrease cerebral blood flow [42,43]. ADMA concentrations in the brain are also negatively correlated with vasodilatory factors (*e.g.*, NO)[44]. Thus, the elevated ADMA levels in the cerebrospinal fluid of patients with subarachnoid hemorrhage (SAH) are believed to be closely related to SAH-mediated vasospasm [45]. Interestingly, PRMTs expression in the brain of SAH patients remains unchanged [45] which suggests that DDAH could be playing a role in vasospasm following SAH. Further studies are necessary to determine the role of arginine methylation in ischemia and cardiovascular disease. Vascular dysfunctions remain closely associated with reduced NO bioavailability [46]. ADMA has been recognized as an important risk factor for cardiovascular and renal disease, including heart failure and type 2 diabetes [47]. Chronically elevated levels of ADMA could lead to prolonged vasoconstriction and hypoperfusion via inhibition of NOS and reduced bioavailability of NO. Consequently,

prolonged cerebral hypoperfusion can lead to cognitive decline and dementia [48]. A reduction in ADMA levels could decrease inflammation and restore vasoactive responses. Overactivity of PRMT enzymes could contribute to these pathological conditions. Therefore, developing a better more specific understanding of PRMT function could lead to a novel therapeutic potential.

PRMT function

PRMT1—PRMT1 is localized in the nucleus and cytoplasm, expressed ubiquitously [49], and is responsible for 85% of all PRMT activity [50]. Furthermore, PRMT1 acts as a transcriptional coactivator and is recruited to promoters by various transcription factors [*e.g.*, p53, nuclear factor- κB (NF-κB)] [51]. Improper PRMT activity can lead to multiple pathologies, including embryogenic dysfunctions, cancer, cardiovascular and neurodegenerative disorders [5,10,52,53]. The embryonic lethality of PRMT1 *in vivo* suggests that its function is critical for cell proliferation and differentiation in multi-cellular organisms [54]. However, a conditional knockout mouse model of *Prmt1*(−/−) is available in specific tissue(s) (*e.g.*, heart, cortex and B cells) [55–57]. The knockout of PRMT1 in the central nervous system resulted in the loss of oligodendrocyte maturation and axon myelination, which indicates that PRMT1 is important for neuronal maturation. The loss of PRMT1 function leads to embryonic defects, including DNA damage, aneuploidy, polyploidy, and cell cycle delay [54] to cause delayed growth, shortened body length and cardiac edema [58].

There are limited studies on the role of PRMT1 in cardiovascular function. Findings in the current literature indicate that PRMT1 functions to preserve cardiac homeostasis and skeletal muscle regeneration [59,60]. Findings from Pyun *et al.* indicate that cardiac-specific ablation of PRMT1 resulted in calcium/calmodulin-dependent protein kinase (CaMK)II hyperactivation to cause dilated cardiomyopathy, cardiomyocyte hypertrophy, and fibrosis to result in heart failure. The same study also reported that PRMT1 expression is downregulated in heart failure patients, which highlights PRMT1's pivotal role in cardiovascular homeostasis [55]. Findings from Kim *et al.* indicate that oxidative stress via hydrogen peroxide results in PRMT1 overexpression [61]. Interestingly, redox control of PRMT1 has been studied by Morales *el. al*, which corroborated and expanded on previous findings to suggest that PRMT1 activity is increased in the presence of reductants and decreased by oxidants [62].

Oxidative stress-induced PRMT1 overexpression inhibited sirtuin1 (SIRT1, a protective enzyme against inflammation) to cause apoptosis in retinal cells [61]. Furthermore, Scalera et al., (2009) reported that red wine (*i.e.* resveratrol) decreased ADMA levels and PRMT1 expression in a SIRT1-dependent manner in human endothelial cells [63]. Further studies are necessary to determine if clearance of ADMA has been affected (*i.e.* DDAH activity). Aberrant overexpression of PRMT1 could reduce SIRT1's protective role against inflammation, heart disease, atherosclerotic plaque development, and apoptosis.

PRMT1 has a controversial role in the apoptotic pathway. PRMT1 methylates Bcl-2-associated death promoter (BAD) protein to prevent its phosphorylation by Akt. BAD, in its dephosphorylated state, inhibits the anti-apoptotic proteins Bcl-2 and Bcl-xL. Consequently,

BAD triggers apoptosis via the release of cytochrome C into the cytoplasm [64]. The knockdown of PRMT1 prevents BAD's inhibition of Bcl-xL and Bcl-2, suggesting that PRMT1 can regulate pro-apoptotic signals. Furthermore, PRMT1 can promote cell survival [64]. The knockdown of PRMT1 via small interference RNA caused an increase in hypoxia-inducible factor 1α and 2 (HIF-1α and HIF-2), which indicates that PRMT1 is an endogenous repressor for both HIF-1α and HIF-2 [65]. HIF-1α activation has been associated to promote adaptive responses to hypoxic stress (e.g., angiogenesis) [66]. However, recent studies also suggest that HIF-1α plays a detrimental role after ischemic injury via the enhancement of apoptotic molecules/cytokines (e.g., Nix and IL-20) to cause mitochondrial dysfunction to results in cell death [67].

Mitochondrial function relevant to PRMT1 has not been well-investigated. Madreiter-Sokolowski et al. claimed that methylation of the mitochondrial calcium uptake 1 (MICU1) via PRMT1 desensitized the transporter to reduce calcium uptake, which indicates that PRMT1 can modulate calcium entry into the mitochondria [68]. Mitochondrial oxygen consumption was also measured by Sha et al. which demonstrated that PRMT1 deficiency reduced oxygen consumption rate and increased reactive oxygen species (ROS) production in the mitochondria [69]. Mitochondrial impairment and ROS formation may result in tissue damage and are closely related with cardiovascular dysfunction [70].

PRMT2 and PRMT4/CARM1—PRMT2 is a type I PRMT enzyme localized in the nucleus, which has been associated to function as a transcriptional repressor [71], inhibits NF-κB-dependent transcription, and promote apoptosis [71]. Knockout of PRMT2 in fibroblasts resulted in increased NF-κB activity and decreased susceptibility to apoptosis [71], suggesting that PRMT2 can regulate pro-inflammatory pathways. PRMT2 expression was enhanced under hypoxic conditions [72]. In addition, PRMT2 interacts with PRMT1 to enhance PRMT1 activity [73]. PRMT2 is also enhanced after hypoxia, which suggests that it can enhance ADMA levels during ischemia[73]. Findings from Zeng et al. indicate that angiotensin II can reduce PRMT2 function and induce the expression of proinflammatory cytokines (30186848). Overexpression of PRMT2 resulted in the inhibition of angiotensin II-induced vascular smooth muscle cell proliferation and proinflammatory cytokines (i.e. IL-6), which suggests that PRMT2 can alleviate angiotensin II-mediate inflammation [74]. Furthermore, PRMT2 deficient bone-marrow-derived macrophages resulted in a reduction in ATP-binding cassette transporter (ABCA1) expression and ABCA1-mediated cholesterol efflux as compared to wild-type [75]. PRMT2 expression was also reduced in diabetic mice, which suggests that PRMT2 has an important role in controlling cholesterol efflux to provide an important insight into atherosclerosis development in diabetic patients [75]. The knockout of PRMT2 resulted in lean, hypophagic mice with reduced serum leptin levels, which suggests that PRMT2 has an important role in obesity and obesity-related syndromes [76]. Furthermore, in neurological function, PRMT2 can methylate the actin nucleator Cobl to regulate neuronal morphogenesis and dendritic arborization in the central nervous system [77].

PRMT4 is another type I PRMT enzyme localized in the nucleus that has a major role in astroglia development and myogenic differentiation [78,79]. The knockdown of PRMT4 caused morphologically abnormal astrocytes, which implies that PRMT4 methylation is

crucial for proper neural development [78]. Moreover, PRMT4 is not only involved in neuronal development but also the late stages of myogenesis via the facilitation of chromatin-remodeling [80]. The knockdown of PRMT4 in muscle stem cells reduced fast muscle fiber formation and restricted slow myosin heavy chain localization. Recently, Wang *et al.* reported that PRMT4 expression was increased in ischemic heart and hypoxic cardiomyocytes [81]. The authors also described that overexpression of PRMT4 in mice induced cardiomyocyte apoptosis to result in a reduction of survival rate, a decrease in left ventricular function, and aggravation of cardiac remodeling after myocardial infarction [81]. Altogether, the roles of PRMT2 and PRMT4 are not well understood in cardiovascular and neurological disease, but both remain a plausible therapeutic target.

PRMT3—PRMT3 is a cytosolic enzyme that is unique for its N-terminal zinc-finger, which confers substrate specificity [82]. In the central nervous system, PRMT3 expression is highly localized to the motor and limbic systems, more specifically within neuronal cell bodies and dendrites [83]. Although PRMT3 knockout mice are viable, they are characterized as abnormally small at an early age but regain normal size in adults, which highlights its role in physical development [84]. Overexpression of PRMT3 and/or PRMT5 was shown to enhance sodium channel 1.5 ($Na_V1.5$) expression in cardiac muscle [41]. Cardiomyocytes overexpressed with PRMT3 sustained action potentials at a higher rate than control, which suggests that abnormal expression of PRMT3 could lead to cardiac excitability to cause cardiac dysfunction. Indeed, PRMT3 was overexpressed in patients with coronary heart disease [35].

In a study to determine PRMT function in hepatic lipogenesis, treatment with palmitic acid caused the translocation of PRMT3 to the nucleus to contribute to subsequent nonalcoholic fatty liver disease [85]. Furthermore, treatment with PRMT3 allosteric inhibitor SGC707 reduced the total accumulation of triglycerides, which indicate a reduction in fatty acid liver disease pathology [86]. Kim *et al.* also suggested that palmitic acid treatment increased ADMA levels, which suggests that PRMT type I activity is enhanced. Indeed, PRMT1 and PRMT3 expression were enhanced after palmitic acid treatment, which implies that fatty acids can modulate PRMT expression [85]. Interestingly, an esterified form of palmitic acid, named palmitic acid methyl ester (PAME) is known to cause potent vasodilation [87]. Moreover, PAME's release is enhanced in the presence of arginine derivatives, which indicates that an arginine-modifying protein (*e.g.*, a PRMT) could play a role in either its synthesis or release [87]. In this regard, PRMTs could contribute to the pathway that leads to the esterification of palmitic acid to form PAME and cause vasodilation [88]. Additionally, PAME is a potential therapeutic agent against cerebral ischemia which enhances post-ischemic cerebral blood flow and reduces neuronal cell death [88,89]. Taken together, PRMT3 represents another promising candidate for the therapeutic study of cardio/neurovascular disease.

PRMT5—PRMT5 is a major type II methyltransferase localized in the cytoplasm and nucleus and is known to be associated with essential cellular processes such as gene regulation, cell proliferation, and differentiation. PRMT5 has been linked to contributing to breast cancer stem cell proliferation and self-renewal, in part through histone methylation to

regulate the transcription factor Forkhead box protein PI (FOXP1) expression [90]. FOXP1 is an essential transcription factor for the migration, dendritic maturation, and morphogenesis of cortical neurons, which suggests that methylation of FOXP1 could affect neuronal development and breast cancer proliferation [91]. Findings from Chiang *et. al.* suggests that small-molecule inhibition of PRMT5 or downstream targets could be an effective strategy to inhibit the proliferation of breast cancer [90]. In cerebral tissue, the knockout of PRMT5 resulted in decreased oligodendrocyte differentiation and severe hypomyelination [92]. Furthermore, PRMT5 can protect against beta-amyloid toxicity in Alzheimer's disease, suggesting that PRMT5 plays an important role in neuronal homeostasis and development [93]. Unsurprisingly, full-body deletion of PRMT5 caused embryonic lethality and is involved in carcinogenesis [94]. Moreover, PRMT5 is upregulated in many cancers, including gastric [95], lung, bladder, colon cancer [96], lymphoma, and leukemia [97,98]. Loss of PRMT5 expression resulted in apoptosis and loss of self-renewal in glioblastomas, indicating that PRMT5 has a pro-oncogenic function. In short, the function of PRMT5 has not been well-studied in neuronal disease states.

PRMT5 is highly expressed in cardiac tissue, which suggests an unknown role in cardiac function. In addition, low expression of PRMT5 in peripheral blood leucocytes increases the likelihood of acute myocardial infarction by ~5500 times [99], which indicates that PRMT5 plays a crucial role against the development of cardiovascular disease. Findings by Chen *et al.* imply that PRMT5 overexpression can reduce GATA4 acetylation, a critical transcription factor for cardiac development in embryos, and cause cardiac hypertrophy [100]. PRMT5 function has not been well-elucidated and studies regarding its role in cardiovascular diseases are conflicting. However, we can predict that PRMT5 could play a role to regulate ADMA and/or SDMA levels. Overall, PRMT5 is another potential candidate for the treatment of cardiovascular diseases *(e.g.,* coronary artery disease, hypertension, and diabetes).

PRMT6 and PRMT7—Although PRMT6, a type I PRMT enzyme localized in the nucleus, has been linked with tumor progression, PRMT6 has yet to be described in neurological and cardiovascular diseases. Scaramuzzino *et al* described PRMT6 as a regulator for polyglutamine disease pathogenesis [101]. Polyglutamine development in androgen receptors is responsible for spinobulbar muscular atrophy, resulting in lower motor neuron degeneration [102]. PRMT6 interaction with a mutant form of the androgen receptor caused neurodegeneration within the spinobulbar pathway, suggesting that PRMT6 has a role in the development of polyglutamine/neurodegenerative disorders. At present, PRMT6 has not been studied in relation to cardiovascular disease.

PRMT7 is a type III PRMT enzyme localized in the cytoplasm and is highly expressed in skeletal muscle [103]. PRMT7 expression in skeletal muscle is reduced with age and obesity. The knockdown of PRMT7 in mice caused reduced oxidative metabolism in skeletal muscle, and mice exhibited decreased exercise endurance [103]. Moreover, PRMT7 null myoblasts reduced peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) expression and PGC-1α-promoter-driven reporter activities [103]. PGC-1α plays a central role in the regulation of cellular energy metabolism via the stimulation of mitochondrial biogenesis and muscle remodeling [104,105]. Therefore, Jeong *et al.*

proposed that PRMT7 is an important regulator for oxidative metabolism via the activation of PGC-1α [103]. Moreover, PRMT7 can also methylate and inhibit sodium leak channels (NALCN) to reduce neuronal excitability, which could be a potential tool in the development of new therapies for seizures [106]. Although PRMT7 has been shown to regulate oxidative metabolism and ion channel function, the function of PRMT7 in cardiovascular and neurological disease is underdeveloped.

PRMT8—In contrast to all other PRMTs, PRMT8 has a highly restricted tissue expression, localized only in neurons in the central nervous system [107,108]. PRMT8 is a unique member of the PRMT family bearing a myristoylation site located on the N-terminus domain, which causes PRMT8 to reside in the cellular membrane [109]. Moreover, PRMT8 shares 80% sequence identity with PRMT1 [53]. PRMT1 and PRMT8 are both involved in the epigenetic control of gene expression and the normal function of neurons [110]. PRMT8 has also been described as a post-translational modifier of various proteins (*e.g.*, Ewing Sarcoma protein, sodium ion channels) [111,112]. Baek *et al.* reported that PRMT8 co-expression with the sodium channel 1.2 ($Na_v1.2$) led to a 3-fold increase in $Na_v1.2$ current, suggesting that arginine methylation could regulate neuronal excitability [113]. Although PRMT8 has been associated with developmental neuroplasticity, motor function, and visual acuity. PRMT8 function has not been well-defined *in vivo* [114].

PRMT8 knockout mice (PRMT8$^{tmla(EUCOMM)Wtsi}$) were used in a study correlating cellular stress and neurodegeneration in aging. Knockout of PRMT8 can cause reduced motor performance, accelerated muscular atrophy and weight loss [115]. Additionally, Kim *et al.* (2015) observed abnormal motor behaviors, including hind limb clasping and hyperactivity in PRMT8 knockout mice [115]. In addition, PRMT8 knockout mice had an increase in DNA double-stranded breaks in aged rats' motor neurons [116]. PRMT8 has also been linked as a component of neuronal stress resistance via the activation of cAMP response-element-binding protein 1 (CREB-1). Lack of PRMT8 results in reduced CREB-1 levels leading to a progressive decrease in muscle strength and decreased cellular viability. Moreover, PRMT8 can act as a phospholipase that hydrolyzes phosphatidylcholine into choline and phosphatidic acid [115]. Phospholipase D2 (PLD2) hydrolyzes lysophosphatidylcholine to generate cyclic phosphatidic acid that inhibits peroxisome proliferator-activated receptor γ (PPARγ). PPARγ activation leads to lipid accumulation, arterial wall thickening, and macrophage recruitment [117]. Thus, PRMT8 could play a similar role as PLD2 in the inhibition of PPARγ.

Overall, the function of PRMT8 has not been well investigated in neuro/cardiovascular diseases. PRMT8 can homodimerize and heterodimerize with PRMT1. The interaction of PRMT1 and PRMT8 could prove to be significant in altering ADMA levels and, consequently NO bioavailability. PRMT8 could be a possible target for the inhibition/regulation of PRMT1 in the central nervous system. Altogether, PRMT1-PRMT8 are both interesting targets for the study of cardiovascular disease.

PRMT9, PRMT10 and PRMT11—Currently, there is no consensus on the exact function or tissue expression of PRMT10 and PRMT11. However, PRMT9 has been well characterized as a nuclear and cytoplasmic type II protein arginine methyltransferase.

Mutations to the PRMT9's catalytic domain can alter its functional properties from a type II to a type III activity. The PRMT9 gene has been linked with pro-oncogenes whose overexpression strongly promotes hepatocellular carcinoma invasion and metastasis [118]. Additionally, PRMT9's protein overexpression was associated with an increase in vascular invasion, poor tumor differentiation, shorter survival time and higher recurrence rate [118]. PRMT9 expression was also significantly decreased in osteosarcoma specimens from patients compared to normal bone tissue [119]. This reduction in PRMT9 expression in osteosarcoma specimens was linked with significantly increased miR-543, which is associated with poor clinical outcomes [119]. The findings from Zhang *et al.* suggest a role for decreased PRMT9 expression in the development of osteosarcoma via glycolysis through an miR-543/PRMT9/HIF-1α axis [119]. Therefore, PRMT9 may serve as a candidate prognostic biomarker and a potential cancer therapeutic target [118]. PRMT9 also functions as a methylator of arginine residues on splicing factor SF3B2 (*i.e.* SAP145) [120]. The splicing factor SF3B2 binds tightly to SF3B4 and has functional roles in cell cycle progression [121]. Previous studies indicate that interference of SF3B2-SF3B4 complex induces G_2 checkpoint arrest, which can eventually cause apoptosis after cell division [121,122]. Overall, the role of PRMT9 has not been described in either cardiovascular or neurological function.

Cell signaling and disease

Post-translational modifications are essential for protein function and signal transduction. PRMTs can modulate biological processes by methylation of nuclear, cytoplasmic, and membrane proteins. Arginine methylation via PRMTs is one of the major types of post-translational modifications that are crucial for biological functions, including nuclear shuttling, DNA repair, mRNA splicing, and signal transduction [51]. Previously, Shen *et al.* (1998) reported the first biological role for arginine methylation, nucleocytoplasmic shuttling in yeast [123]. The transport mechanism is dependent on interactions with the nuclear envelope, which facilitates the transport of nuclear proteins into the nucleus and the export of RNA to the cytoplasm. The spatial separation of mRNA between synthesis and translation allows for a high complexity in gene regulation and expression. The binding of RNA to specific proteins termed RNA-binding proteins (RBP), allow for the stabilization, modification, and translocation of RNA. PRMT1 and PRMT4 can methylate RBPs at multiple glycine-arginine-rich and proline-glycine-methionine motifs, respectively [51]. Additionally, the methylation of proteins can affect their intracellular distribution. For instance, inhibiting the methylation of high molecular weights of fibroblast growth factor-2 (FGF2) and the Src-Associated substrate in Mitosis of 68kDa (Sam68), an RNA bridging protein, results in a decrease in their nuclear accumulation [51,124]. Moreover, the adenovirus 100K methylated protein is exclusively nuclear, however, treatment with methylation inhibitors prevent adenovirus 100K protein from localizing in the nucleus and to accumulate in the cytoplasm [125] [126]. Interestingly, hypomethylated proteins are unable to freely cross the nuclear membrane accumulating in both nucleus and cytoplasm. This suggests that arginine methylation is necessary for nuclear localization and signaling.

In addition, arginine methylation has been strongly linked to RNA turnover, metabolism, transcription, and splicing. PRMT4 (CARM1) has been described to methylate the mediator

complex subunit 12 (MED12) and the lysine methyltransferase KMTD2, which are enhancers for mRNA splicing [127,128]. Additionally, RNA splicing efficiency is reduced in hypomethylated nuclear extracts. PRMT4 is responsible for the methylation of a variety of splicing factors including CA150, U1C and SAP49 [129]. The methylation of CA150 generates a docking motif for the survival of the motor neuron Tudor domain.

PRMTs have also been linked with DNA repair. DNA double-stranded breaks that are caused by ionizing radiation or replication error are repaired endogenously via base excision repair, nucleotide excision repair, and double-stranded break repair. Additionally, homologous recombination repair (HRR) and non-homologous end joining (NHEJ) are complexes responsible for DNA repair in eukaryotes. The Mre11/Rad50/Nbs1 complex (MRN) is important in the initiation of HRR DNA repair [130]. Furthermore, Mre11 is the only known protein in the MRN complex that has a glycine-arginine rich motif. Hypomethylated Mre11 severely impaired its activity, to suggest that PRMT1 can methylate Mre11, thereby promoting regulation of DNA damage checkpoints [131]. Furthermore, global methyltransferase inhibition prevented Mre11 from being recruited to double-strand breaks, indicating that methylation of Mre11 regulates MRN localization to double-strand DNA breaks [131]. PRMT5 can also function as a regulator for homologous recombination-mediated double-strand break repair [132]. PRMT5 is responsible for the methylation of RuvB-like 1(RUVBL1), a coactivator of the TIP60 complex, to promote HRR [132]. Cells also depend on other mechanisms for DNA repair, including base excision repair, which is required for endogenous DNA maintenance, recombination, and replication. DNA polymerase β Pol-β) is responsible for base excision repairs and its lyase domain is related to PRMT1 and PRMT6 [133]. PRMT1 can methylate the arginine residue R137 in Pol-β to inhibits its interaction with proliferating cell nuclear antigen (PCNA) and endogenous DNA maintenance [134]. Additionally, PRMT6 can methylate the arginine residues R83 and R152 of Pol-β to enhance Pol-β activity and binding to DNA [133]. Altogether, arginine methylation remains not well understood in the context of DNA repair, mRNA splicing, and nucleocytoplasmic shuttling.

The role of PRMTs in neurological disease

While PRMTs play a crucial role in many cellular functions, they are also implicated in the pathogenesis of different diseases, including glioblastomas, amyotrophic lateral sclerosis, and Huntington's disease [5,135]. Glioblastomas are an aggressive type of malignant grade IV tumors that arise from astrocytes. Findings from Yan *et. al.* suggests that PRMT5 is overexpressed in primary glioblastoma tumors via histone methylation to silence the transcription of regulatory genes [136]. PRMT5 depletion has also been reported to increase the expression of p27 (an inhibitor of cyclin-dependent kinase) through the PTEN-AKT pathway and activate retinoblastoma protein, a tumor suppressor, to cause cell cycle arrest leading to cancer senescence [137]. Several studies have suggested that small-molecule inhibitors of PRMT5 are potential therapeutic strategies against neuroblastomas or glioblastomas [138–140]. Currently, there are clinical studies investigating the effects of PRMT5 inhibitors in brain tumors (clinical trial identifiers NCT03573310, NCT02783300, and NCT03614728).

In the central nervous system, PRMTs have been described to play a role in cell maturation/ differentiation. neurodegeneration, and synapse composition/function [6,57,141,142]. Nevertheless, the physiological significance of PRMTs in the brain remains unclear. For example, abnormal brain morphologies (*e.g.*, small and malformed brain) and loss of neurons can be observed in PRMT8-knockdown zebrafish. Among other PRMTs, Bezzi *et al.* proposed that conditional knockout of PRMT5 (PRMT5$^{-/-}$) in the central nervous system ablated neural stem self-renewal function, which reduced the number of cells in the dorsal telencephalon as compared to control animals [142]. Numerous studies also emphasize that PRMT1 and PRMT5 can promote oligodendrocyte maturation and axon myelination via inhibition of differentiation repressors (*e.g.*, Id2 and Id4) [57,92,141]. Interestingly, findings from Selvi *et al.* indicate that PRMT4 can modulate several microRNAs (*e.g.*, miR-92a, miR-10a, and miR-575) that are responsible for cell-specific differentiation events (*e.g.*, astroglial differentiation) [78], while inhibition of PRMT4 in embryonic stem cells can cause loss of astroglial lineage [78]. Hence, inhibition/loss of PRMT1, 4, and 5 are highly associated with neurodegenerative, demyelinating disease, and multiple sclerosis [57,143]. These studies indicate PRMTs' essential role in the development of the nervous system [144].

In addition to neural stem cell maturation/differentiation, PRMTs have also been reported to be involved in synapse composition and function. For example, Penney *et al.* suggested that PRMT8 is a neuronal-specific synaptic protein that can post-translationally modulate various synaptic vesicle proteins (*e.g.*, synapsin, synaptophysin, presynaptic regulators *N*-ethylmalcimide-sensitive factor, synaptotagmin, and complexin) [114]. Thus, the deletion of PRMT8 reduces synaptic transmission in the hippocampus [114]. Additionally, PRMT8 has been shown to play a role in synaptic maturation and neural plasticity. Findings by Lee *et al.* illustrated reduced dendritic brandling and neuroplasticity in PRMT8 knockout mice [145]. Furthermore, it has been well-defined that synaptic transmission between CA1 and CA3 regions of the hippocampus plays an essential role in learning and memory formation [146], which highlights the importance of PRMT8 in functional learning/memory.

Interestingly, ion channel dysfunctions have been linked with various vascular diseases which indicate that PRMTs could play a role in both cardiovascular and neurological diseases [147]. Recently, PRMTs have also been linked to control neuronal excitability through the methylation of potassium and sodium leak channels. Findings from Kim *et al.* suggest that arginine methylation of the potassium voltage-gated channel subfamily Q member 2 (KCNQ2) by PRMT1 could positively regulate KCNQ activity by enhancing its binding to PIP2 to prevent neuronal hyperexcitability and seizures [38]. Moreover, a recent study by Lee *et al.* suggests that PRMT7 can methylate NALCN at R1653 in the hippocampus to inhibit NALCN function thereby reducing neuronal excitability [106].

PRMTs have also been implicated in regulating cell survival in neurodegenerative disease states such as amyotrophic lateral sclerosis (ALS). In ALS, the cytosolic accumulation of FUS protein bodies in motor neurons has been associated with neurodegeneration [148]. Scaramuzzino *et al.* reported that the abolition of PRMT1 and PRMT8 resulted in augmented neurodegeneration in a *Drosophila* model of ALS. Furthermore, it has been proposed that neuronal PRMT enhances methylation of the FUS protein, which prevents its

aggregation to attenuate the development of ALS [53]. Suarez-Calvet *et al.* also suggested that *in vitro* PRMT1 activity is crucial in the methylation and inactivation of FUS-protein binding affinity to transportin [149]. Downregulation of PRMT 1-8 in the central nervous system could affect their function on posttranslational methylation of proteins, which may be a critical factor in neurodegenerative pathologies [108].

Among the various neurodegenerative pathologies, PRMT5 has been associated with Alzheimer's disease [93]. Quan *et al.* first identified the regulatory interactions between beta-amyloid (the major pathological component of amyloid plaques found in Alzheimer's patients' brains) and PRMT5 [93]. The authors proposed that beta-amyloid can inhibit PRMT5 expression in neurons via E2F-1 (a PRMT5 target protein)-mediated pathways [93]. Moreover, knockout of PRMT5 in SH-SY5Y neuroblastoma cells overexpressing mutant beta-amyloid precursor protein (an *in vitro* model of Alzheimer's disease) further activates nuclear factor-κB, and glycogen synthase kinase 3 beta pathways, to cause apoptotic cell death [93]. Altogether, these results indicate PRMT5's novel neuroprotective role and potential therapeutic effects against beta-amyloid toxicity.

Modulation of PRMTs

Initially, PRMT inhibitors were categorized under a series of arginine methyltransferase inhibitors (AMIs) from 1 to 9. AMIs are symmetrically sulfonated ureas that specifically inhibit PRMT activity. Currently, there are 9 different subtypes of AMIs, but the most well-characterized is AMI-1. AMI-1 is cell-permeable and able to inhibit endogenous cellular PRMT type I activity. AMI-1 has been previously used to reduce PRMT type I activity to investigate PRMT1's role in pulmonary inflammation in a rat model of asthma. The findings indicate that inhibition of PRMT1 reduced expression of eotaxin-1 (eosinophil chemotactic protein) and ameliorated pulmonary inflammation [150], which suggests that PRMT type I function could be involved in inflammatory responses. Indeed, the treatment of rats with AMI-1 inhibited cyclooxygenase-2 (COX-2) expression, mucus secretion, collagen generation, and humoral immune response [151]. Additionally, COX-2 is inducible in inflammatory settings and functions to further promote inflammation, which indicates that COX-2 plays an instrumental role in neurodegenerative diseases [152]. Furthermore, inhibitors of COX-2 have been reported to reduce brain injury in response to global ischemia and excitotoxicity [153,154]. Therefore, if AMI-1 can inhibit COX-2 response, AMI-1 could prove to be neuroprotective after neuronal stress *(e.g.*, ischemia and Alzheimer's disease).

MS023 has been reported by Eram *et al.* as another PRMT type I inhibitor [155]. The authors designed MS023 based on the recent discoveries of EPZ020411, a potent and selective PRMT6 inhibitor, and CMPD-1, a PRMT4 (CARM1) inhibitor [155]. Furthermore, their results suggest that MS023 can selectively inhibit type I PRMTs, including PRMT1, 3, 4, 6, and 8, and is inactive against type II and type III PRMTs, protein lysine methyltransferases, and DNA methyltransferases [155]. Treatment of cells with MS023 reduced ADMA and increased MMA and SDMA levels, indicating that inhibition of type I PRMTs shifts methylation activity towards type II and type III PRMT activities. The shift in methylation activity of PRMT types is an exciting topic in the study of arginine methylation,

leading to several excellent publications in various scientific fields, including biochemistry, cancer, and physiology [155–157].

Arginine methylation can also be inhibited non-specifically via the product inhibitor of the reaction, *S*-adenosyl-L-homocysteine (AdoHcy or SAH). AdoHcy is formed by the demethylation of *S*-adcnosyl-L-methionine (AdoMet or SAM) [6]. Moreover, AdoHcy is a potent inhibitor of AdoMet-dependent methylation reactions [158] and has been reported to be a methyltransferase inhibitor [159–161], and associated with cellular hypomethylation [162]. Esse *et al.* suggested that the accumulation of intracellular AdoHcy reduces general protein methylation [163]. Furthermore, their results suggested a 2.5-fold increase of AdoHcy levels if the breakdown of AdoHcy was inhibited via AdoHcy hydrolase inhibition. An increase in AdoHcy caused a 10% decrease in all arginine methylation [163]. Non-specific inhibition of arginine methylation does not appear to represent a viable technique in the investigation of arginine methylation function in cardiovascular and neurological disease.

Competitive small-molecule inhibitors are promising targets for the specific inhibition of PRMT enzymes [164]. For instance, PRMT5 inhibition is one of the most promising anticancer targets in the PRMT family [165]. Inhibitors have been designed to inhibit the AdoMet binding pocket domain [166]. The synthesis of specific inhibitors is essential to further our understanding of PRMT activity and function in normal and pathological scenarios. Altogether, the discovery of more specific and potent PRMT inhibitors are needed to elucidate the role of PRMTs in neurological and cardiovascular disorders.

CONCLUSION

Arginine methylation has emerged as a potential therapeutic target for cardiovascular and neurological diseases. Interestingly, PRMTs are responsible for the generation of the NOS inhibitor ADMA. Dysregulation of PRMT function can increase ADMA levels, which inhibits NO production to cause endothelial dysfunction and neurovascular disease. In the brain, PRMTs are involved in neuronal maturation and differentiation, and loss of PRMT function has been associated with neurodegenerative diseases. The metabolic balance of PRMT activity could prove to be beneficial for both cardiovascular and neurological diseases. Therefore, PRMTs are a promising therapeutic target for the study of cardiovascular and neurological diseases.

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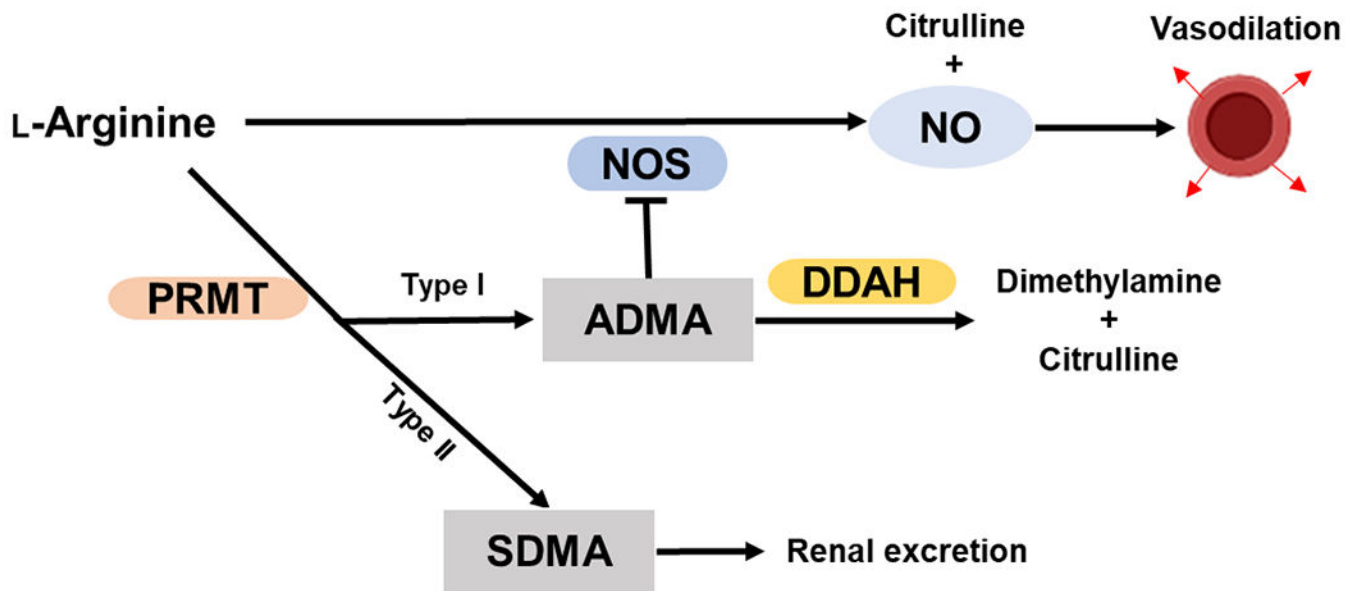
Figure 1. Protein Arginine Methylation and Nitric Oxide Regulation.
Arginine is the substrate for nitric oxide synthase (NOS) to generate nitric oxide, a regulator of vascular function and homeostasis. Arginine can also be methylated by protein arginine methyltransferases to form asymmetric dimethyl arginine (ADMA) and symmetric dimethylarginine (SDMA). ADMA inhibits the synthesis of nitric oxide, resulting in vascular dysfunction. Cardiovascular disease treatments can employ strategies around impacting PRMT activities and/or ADMA levels.
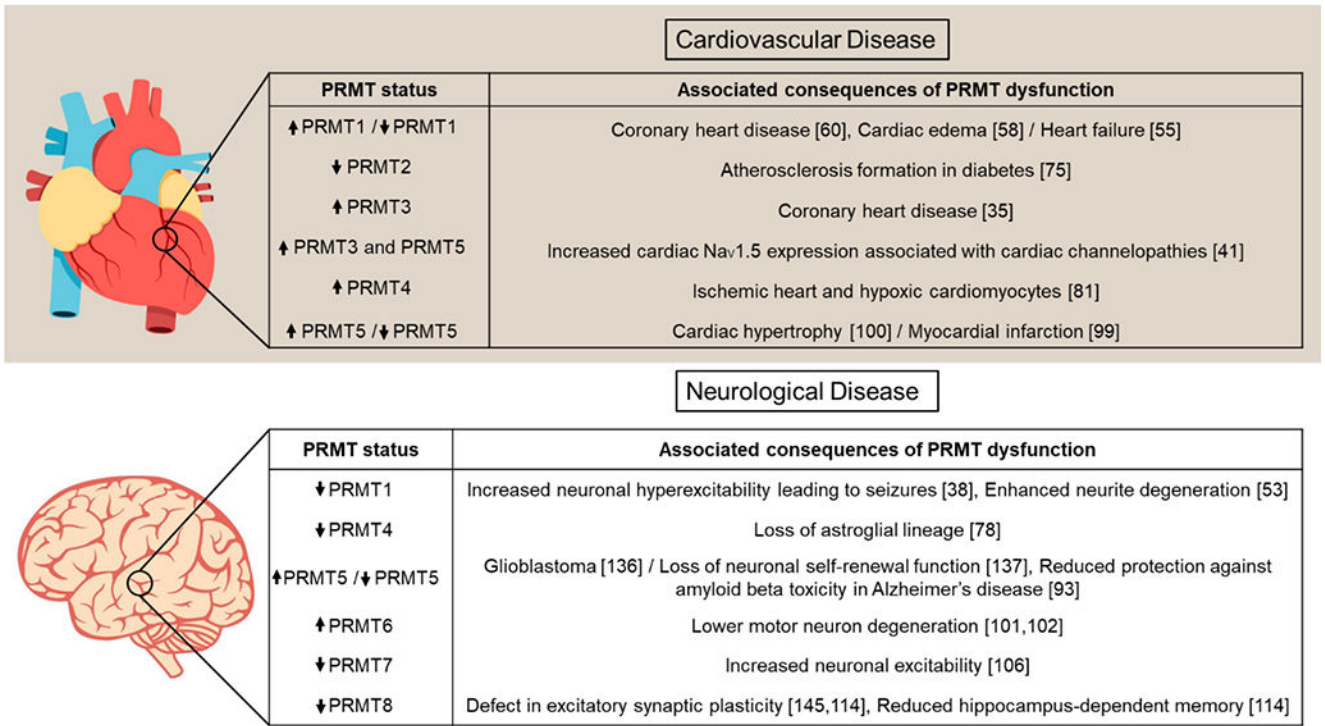
Figure 2.
Cardiovascular and neurological diseases associated with PRMT dysfunctions.

Table 1:

Protein arginine methyltransferase tissue expression, knockout phenotype and function

PRMT species	Tissue type	Knockout phenotype	Function
PRMT1 [54]	Adrenal, Brain, Cerebellum, Colon, Esophagus, Frontal cortex, Heart, Dendritic cell, Kidney, Liver, Lung, Ovary, Pancreas, Retina, Stomach, Testis, Thyroid, Urinary bladder	Embryonically lethal with abnormal morphology	Epigenetic transcriptional activation of estrogen receptor, transcriptional activity, neurite outgrowth, megakaryocytic differentiation and ubiquitination
PRMT2 [71]	Serum, Testis	Hyperplastic response to vascular injury	Coactivator of androgen and estrogen receptor mediated transactivation, inhibits NF-κB transcription, promote apoptosis, repress transcriptional activity, growth regulation.
PRMT3 [84]	Adrenal, Heart, Liver, Ovary, Brain	Reduced embryonic size survives to adulthood to attain nonnal size	Regulates ribosomal biosynthesis, substrate recognition, interactions associated with tumor suppressor proteins
PRMT4 [78]	Adrenal, Cerebellum, Colon, Esophagus, Frontal cortex, Gall bladder, Kidney, Liver, Lung, Ovary, Pancreas, Stomach, Testis, Thyroid, Urinary bladder	Small fetuses die perinatally	Modulates DNA packaging, transcription regulation, pre-mRNA splicing, mRNA stability, chromatin remodeling, transcriptional activator
PRMT5 [94]	Adrenal, Bile, Brain, Cerebellum, Colon, Esophagus, Frontal cortex, Gall bladder, Heart, Dendritic cell, Kidney, Liver, Lung, Ovary, Pancreas, Retina, Stomach, Testis, Urinary bladder	Embryonically lethal before somite formation	Modulates transcriptional elongation, assembly of small nuclear ribonucleoproteins, cytokine-induced transduction pathways, cellular proliferation, migration and differentiation, transcriptional corepressor.
PRMT6 [101]	Adrenal, Liver, Ovary	Decreased embryonic fibroblast proliferation displayed with early cellular replicative senescence	Regulates DNA base excision repair, alternative splicing, transcriptional coactivator, steroid hormone receptors, promotes fasting induced transcriptional activation, innate immunity against HIV-1, protection from ubiquitination and degradation.
PRMT7 [103]	Brain, Lung, Testis	Decreased expression of oxidative metabolism genes, decreased oxidative metabolism in muscles, reduced exercise endurance, decreased energy expenditure leading to obesity	Assists in the assembly of snRNP core particles, gene imprinting, embryonic stem cell pluripotency.
PRMT8 [114,115]	Brain	Displays abnormal Purkinje cell dendrite morphology, hyperactivity, limb grasping, gait abnormalities, reduced levels of acetylcholine and choline, and increased phosphatidylcholine levels in the cerebellum	DNA repair, RNA transcription, signal transduction, protein compartmentalization.
PRMT9 [167]	Liver	Decreased total body fat amount, increased threshold for auditory brainstem response, increased bone mineral content	Regulates alternative splicing of pre-mRNA, modulator of small nuclear ribonucleoprotein maturation