Relationship between protein arginine methyltransferase and cardiovascular disease (Review)

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Abstract. Protein arginine methyltransferases (PRMTs) are widely found in eukaryotes and regulate gene expression and post-translational modifications. PRMT1-PRMT6 have important roles in the pathology of cardiovascular diseases (CVDs), including atherosclerosis, heart failure and myocardial hypertrophy. Although these enzymes are also closely associated with various CVDs, the mechanisms of the involvement of PRMTs in the regulation of CVD have remained largely elusive. PRMTs methylate arginine residues and other factors. The present review describes the roles of PRMT1-PRMT6 in CVD. Furthermore, the biological characteristics of PRMTs and mechanisms by which PRMTs regulate cholesterol metabolism are being introduced. This review aims to provide inspiration for cardiovascular drug research and offer clues for research on the pathogenesis of CVD.

Contents

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1. Introduction

Protein arginine methyltransferases (PRMTs) are methylases that are widely present in numerous organisms. Their main biological function is to mediate arginine methylation modification, a post-translational modification that commonly occurs in the nucleus and cytoplasm. In recent years, the modification of arginine methylation and its related mechanisms have received increasing attention. Although arginine methylation products were detected in nuclear extracts in 1996, the genes encoding PRMT-related proteins were only identified in recent years (1).

Cardiovascular disease (CVD) is currently among the most serious threats to human life and health worldwide (2). Its morbidity and mortality exceed those of other tumor diseases and are ranked first. Common CVDs include hypertension, atherosclerosis (AS), heart failure, hyperlipidemia and coronary heart disease, which are associated with high morbidity, disability, mortality and serious complications (3). As PRMTs and CVD are closely related, clarifying their relationship and the mechanisms of PRMTs is important for reducing the incidence of CVD and improving human health.

In addition, arginine methylation is increasingly associated with cancer progression. As they perform arginine methylation, PRMTs regulate post-translational modification of proteins that are vital for increasing proteome diversity and maintaining cellular homeostasis (4). Protein arginine methylation is an abundant modification that may involve processes including gene transcription, signal transduction, DNA repair and mRNA splicing. Studies have recently linked this modification to carcinogenesis and metastasis (5).

2. Biological characteristics of PRMTs

Epigenetics represents a wide range of gene expression changes (6), the mechanisms of which include DNA methylation or demethylation, histone methylation or demethylation, histone acetylation or deacetylation and non-coding RNA. The processes of gene transcription or silencing, signal transduction, DNA repair and DNA replication are mediated by chromatin composed of DNA and histones (H2A, H2B, H3 and H4) (7,8). As a type of epigenetic process, histone methylation is one of the most common post-translational modifications of histone, which is usually related to transcriptional activation or inhibition of downstream genes (9). The methylation of arginine may be catalyzed by PRMTs (10).

Arginine methylation is a process in which the nitrogen atom of arginine in a polypeptide is modified by a methyl group in a reaction catalyzed by nine PRMT enzymes (11). PRMTs catalyze the transfer of a methyl group from S-adenosyl methionine to the terminal guanidine nitrogen atom of arginine to produce methyl arginine and S-adenosine homocysteine (12).

PRMTs catalyze arginine to form three different amino acids: Monomethyl-arginine (MMA), asymmetric dimethylarginine (ADMA) and symmetric dimethyl-arginine (SDMA) (13). ADMA is formed by connecting two methyl groups to one terminal nitrogen atom, SDMA is formed by connecting one methyl group to each guanidine nitrogen atom at the end of the arginine and MMA is formed by connecting a single methyl group to a terminal nitrogen atom (14). In addition, PRMTs catalyze non-histone substrates, e.g., PRMT1 methylates RNA-binding proteins (eukaryotic translation initiation factor 4A, infected cell protein 27 and polyadenylate binding protein 1) and transcription factors Twist1, TATA-box-binding protein-associated factor 15, CCAAT enhancer-binding protein α, runt-related transcription factor 1 and transcription factors (7).

Based on the different catalytic products, PRMTs may be divided into three types: Type I PRMTs are involved in the catalytic synthesis of MMA and ADMA, and include PRMT1-3, PRMT6, PRMT8 and arginine methyltransferase 1 (CARM1 or PRMT4); type II PRMTs are involved in the catalytic synthesis of MMA and SDMA, and include PRMT5, PRMT9; and type III PRMTs are involved in the catalytic synthesis of MMA, which is mainly limited to the production of methyl methacrylate by PRMT7 (10,15).

PRMTs participate in numerous cellular processes as epigenetic regulators. For instance, PRMT2 was reported to be overexpressed in several cancer types, such as breast cancer and glioblastoma, as well as during cellular processes, such as inflammatory response, Wnt signaling, cell growth and apoptosis (16). PRMT5 catalyzes the symmetrical dimethylation of histones and arginine residues in numerous non-histone proteins, thereby regulating RNA splicing and suppressing gene transcription (17). PRMTs are also closely related to various diseases. PRMT3 was observed to be involved in the accumulation of liver triglycerides dependent on liver X receptors (LXRs) *in vivo* and in processes of CVD (18). PRMT7 has a key role in the self-methylation-induced epithelial-mesenchymal transition process and promotes the migration and invasive behavior of breast cancer cells (19). In recent years, studies have focused on the role of PRMTs in CVD. The following will introduce the role of PRMTs in the occurrence and development of CVDs; these roles are outlined below based on the relationship between PRMTs, cholesterol metabolism and CVD. As presented in Table I, to clarify the roles of PRMT1-PRMT6 in CVDease, the characteristics, mediating factors and related roles of each PRMT are listed.

3. PRMTs and cholesterol metabolism

PRMT2 promotes cholesterol efflux. PRMT2, also known as heterologous ribonucleoprotein methyltransferase 1, is a key member of PRMTs and is located on chromosome 21q22.3 (20). PRMT2 is widely present in various tissues of the human body, exhibiting high expression in various tissues, including the blood vessels, heart and nervous system. It mainly functions as an auxiliary activator that interacts with a variety of nuclear proteins and participates in RNA metabolism and transcriptional regulation, such as in group protein methylation (21).

ATP-binding cassette transporter A1 (ABCA1) and ABCG1 are members of the ABC superfamily, which are involved in cholesterol metabolism, removing excess cholesterol from cells and preventing AS (22). It has an important role in mediating the transmembrane transport of cholesterol and proteins by consuming ATP. Li *et al* (23) indicated that overexpression of PRMT2 significantly increased the expression of ABCA1 and reduced cholesterol levels in macrophages induced by oxidized low-density lipoprotein (ox-LDL), thereby affecting the efflux of cholesterol and degradation of macrophage-derived foam cells. The mechanism of these effects are related to inhibition of ox-LDL in RAW 264.7 macrophages by PRMTs, which are involved in forming foam cells induced by cholesterol efflux mediated by ABCA1 and ABCG1.

Glomest first proposed the concept of reverse cholesterol transport (RCT), which is the only means by which the body is able to excrete excess cholesterol (24). Studies have indicated that RCT dysfunction is involved in the occurrence and development of AS; determining the molecular regulatory mechanism of RCT may provide new ideas for the prevention and treatment of CVD (25). ABCA1 has a key role in RCT by mediating the transfer of intracellular cholesterol to apolipoprotein A1 (ApoA1). The accumulation of cholesterol in macrophages may increase the expression of ABCA1 and cooperate with ABCG1 to increase the outflow of cholesterol and promote the formation of RCT (26), which is meaningful for reducing accumulated cholesterol in the blood vessel wall (27). As an important mediator of ABCA1 and potential regulator of LXR, PRMT2 regulates LXR-mediated ABCA1 expression and ABCA1-dependent cholesterol efflux (28). Overexpression of PRMT2 enhances ABCA1 gene expression, whereas ABCA1 gene expression decreases upon PRMT2 depletion. In PRMT2 knockout macrophages, which exhibit defects in ABCA1 upregulation and cholesterol efflux to ApoA1, AS is more likely to occur because the cells cannot effectively drain cholesterol. Therefore, it is essential to understand the role of PRMT2 in LXR-mediated AS.

Cardiac hypertrophy is a common sign of CVD, which refers to two changes of cardiac chamber dilatation or cardiac wall hypertrophy, collectively referred to as cardiac

Table I. Role of PRMT1-PRMT7 in CVD.

PRMT enzyme	Type	Arginine methylation	Mediating factors	Role in CVD	(Refs.)
PRMT1	I	MMA and ADMA	CaMKII	Inhibits myocardial hypertrophy by inhibiting CaMKII	(10,15,49)
PRMT1	I	MMA and ADMA	PIP2	Prevention of heart failure by reducing IKs and extending the duration of ventricular action potentials	(10,15,50)
PRMT2	I	MMA and ADMA	LXRs	Promotion of RCT by increasing the expression of ABCA1 and ABCG1	(10,15,22,28)
PRMT3	I	MMA and ADMA	LXRs	Promotion of RCT by increasing the expression of ABCA1 and ABCG1	(10,15,30,33,46)
			H4 and ox-LDL	Induction of the occurrence of AS by inhibiting the production of intracellular NO	(7,10,15,28,44,46,47)
PRMT4	I	MMA and ADMA	BCL2-associated X	Evasion of cardiomyocyte apoptosis by modulating Bax	(10,15,52)
PRMT5	II	MMA and SDMA	SREBP1	Promotion of the expression of genes associated with cholesterol biosynthesis	(10,15,36,37.39)
PRMT5	II	MMA and SDMA	GATA4	Inhibition of cardiomyocyte cell masting by inhibiting the transcriptional activity of GATA4	(10,15,57-59,61)
§PRMT5	II	MMA and SDMA	O-GlcN	Prevention of DCM by inhibition of protein O-GlcN acylation	(10,15,53)
PRMT6	I	MMA and ADMA	H3R2Me2a	Enhancement of the expression of atrial natriuretic peptide	(10,15,63-65)
PRMT7	III	MMA	β-catenin	Inhibition of the Wnt/β-catenin pathway by regulating methylation of β-catenin and thus myocardial hypertrophy	(10,15,67,68)

PRMTs, protein arginine methyltransferases; MMA, monomethyl-arginine; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethyl-arginine; CaMKII, calmodulin-dependent protein kinase II; LXRs, liver X receptors; RCT, reverse cholesterol transport; ABCA1, ATP-binding cassette transporter A1; H4, histone protein-4; ox-LDL, oxidized low-density lipoprotein; AS, atherosclerosis; NO, nitric oxide; SREBPs, sterol-regulatory element-binding proteins; LOX-1, ox-LDL receptor-1; IKs, slow delayed rectifier potassium current; PIP2, phosphatidylinositol 4,5-bisphosphate; DCM, dilated cardiomyopathy; CVD, cardiovascular disease.

hypertrophy. It is important for the differential diagnosis and prognosis of CVD to correctly determine the location and degree of cardiac hypertrophy.

While cardiac hypertrophy may have numerous causes, hypertensive heart disease and coronary AS heart disease are the most common ones. The elevated cholesterol caused by abnormal cholesterol metabolism and excretion increases the incidence of coronary heart disease and markedly increases the occurrence of AS (18).

PRMT2 is closely related to the occurrence and development of AS (23). Studies have indicated that macrophages of mice lacking PRMT2 are more prone to AS due to their inability to efficiently excrete cholesterol (28). The influence of cholesterol efflux in macrophage-derived foam cells by PRMT2 overexpression inhibits the deposition of cholesterol in macrophages and the formation of foam cells, which is considered to be an important pathway against AS (23). Severe hypercholesterolemia leads to stenosis of the lumen, resulting in persistent damage, which in turn leads to systemic AS, resulting in myocardial ischemia and coronary heart disease. In severe cases, acute myocardial infarction aggravates CVD, which causes the heart to enlarge.

PRMT3 regulates cholesterol synthesis and efflux. The unique 'zinc finger' structure at the N-terminus of PRMT3 distinguishes it from other arginine methyltransferases, indicating possible unique functions. PRMT3 has an important role in several biological processes in the body. In recent years, PRMT3 has been considered a new target for anti-AS and CVD treatment. Studies are required to explore the role of PRMT3 in these diseases.

LXRs, which are members of the nuclear receptor superfamily, are cholesterol receptors in the body. These receptors promote cholesterol efflux by increasing the ABC transporter subtype and control processes such as absorption, metabolism, transport and decomposition. LXR is essential for cholesterol metabolism in the liver and macrophages and is considered an important target for treating disorders related to cholesterol metabolism (29). PRMT3 is considered a specific coactivator of LXR-mediated cholesterol metabolism and LXR transcription

cofactor. PRMT3 regulates LXR-mediated cholesterol metabolism by upregulating the expression of ABCA1 and ABCG1, thereby maintaining cholesterol homeostasis in macrophages (30).

Kim *et al* (31) indicated that inhibiting the function of PRMT3 prevents the accumulation of triglycerides in hepatocytes, destroys the ability of LXR to stimulate adipogenesis and relieves the driving effect of LXR on cholesterol metabolism and LXR-mediated fatty acid and cholesterol metabolism. As a common high-efficiency inhibitor of PRMT3, SGC707 reduces LXR activity by inhibiting PRMT3, which weakens the degree of liver steatosis. Chronic treatment of hyperlipidemia ApoE-knockout mice with the allosteric PRMT3 inhibitor SGC707 effectively reduced the degree of hepatic steatosis and significantly reduced the expression level of lipoprotein lipase mRNA in adipocytes (32). This finding indicates that PRMT3 is an intermediate factor that strongly and selectively affects the activity of LXR in hepatocytes. The direct combination of LXR signals strengthens transcriptional assistance and regulates liver adipogenesis. Overexpression of PRMT3 may increase the expression of lipogenic proteins, whereas PRMT3 silencing and PRMT3 knockout in mouse embryonic fibroblast cell lines was indicated to reduce the expression of lipogenic proteins (33).

PRMT3 is considered a novel target in human AS and CVD. PRMT3 has a key role in cholesterol-driven pathologies, such as AS (30). The accumulation of systemic cholesterol and increased susceptibility to AS caused by PRMT3 may increase the burden on the heart, affecting normal blood circulation. This may lead to hardening of the arteries, promoting the deposition of cholesterol and fat in the arterial intima and forming AS plaques. The degree of stenosis increases significantly and promotes the formation of AS, which is also considered to be the pathological basis of coronary heart disease. It may lead to the occurrence of cardiac hypertrophy or aggravate the original degree of cardiac hypertrophy, which is not conducive to the control and treatment of heart disease.

PRMT5 promotes cholesterol biosynthesis and metabolism. PRMT5 is the main type II protein arginine methyltransferase that catalyzes the symmetrical transfer of two methyl groups to histones and functions by binding to specific proteins in the nucleus and cytoplasm (34). PRMT5 controls a variety of metabolic pathways, including the metabolism of cholesterol, fatty acids, other lipids and amino acids but exerts its strongest impact on cholesterol metabolism. Studies have indicated that the expression of PRMT5 in activated T-cells is necessary for the expression of cholesterol biosynthesis- and metabolism-related genes (35). The expression of cholesterol metabolism-related genes in PRMT5-knockout T cells was indicated to be reduced by ~42%, whereas in T-helper cells lacking PRMT5, ~75% of the cholesterol biosynthesis pathway was inhibited (36). These results indicate that PRMT5 controls T-cell cholesterol metabolism and regulates the expression of various enzymes involved in the cholesterol pathway.

Sterol-regulatory element-binding proteins (SREBPs) are essential for maintaining the balance between protein and lipid biosynthesis, and SREBP transcription factors regulate lipid and sterol biosynthesis (37). Three subtypes of SREBP have been identified in mammals. Among them, SREBP1 is mainly involved in regulating fatty acid, triglyceride and phospholipid synthesis genes, and SREBP2 is involved in activating cholesterol synthesis genes and enhancing cholesterol biosynthesis (38).

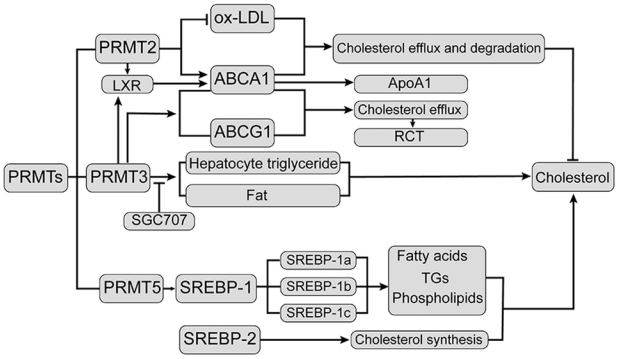

Figure 1. Relationship between PRMTs and cholesterol. Overexpression of PRMT2 lowers ox-LDL-induced macrophage cholesterol levels, significantly increasing the expression of ABCA1 and thus affecting cholesterol efflux and degradation. LXR is a cholesterol receptor in the body that promotes cholesterol outflow by increasing ABCA1 and controlling cholesterol absorption, metabolism, transport and decomposition. SGC707 is a common phosphorylation PRMT3 high-efficiency inhibitor; through inhibition of PRMT3 to reduce LXR activity, it may prevent the accumulation of liver cell TGs and destroy the capacity of LXR to stimulate fat production. PRMT5 interacts with SREBP1 in an enzyme-based manner, involving the regulation of fatty acids, TGs and phospholipids to regulate cholesterol synthesis. SREBP2 is involved in activating the cholesterol synthesis gene to enhance the biosynthesis of cholesterol. PRMT2, protein arginine methyltransferase 2; ox-LDL, oxidized low-density lipoprotein; LXR, liver X receptor; SREBP1, sterol-regulatory element binding protein 1; TGs, triglycerides; Apo, apolipoprotein; ABCA1, ATP binding cassette subfamily A member 1.

Studies have indicated that PRMT5 enhances the stability of SREBP1 by promoting the expression of SREBP1 and cholesterol biosynthetic pathway-related enzymes, thereby regulating cholesterol synthesis (39). PRMT5 is overlapped and co-purified with SREBP to increase its transcriptional and enzymatic activity and interacts with SREBP1 in an enzyme activity-dependent manner, which includes arginine methylation modification and inhibition of proteasome enzymatic degradation. PRMT5 inhibits the phosphorylation and proteasomal degradation of SREBP1 by methylating it at R3231, stabilizing the cleavage nucleus form of SREBP1 in T cells, increasing the synthesis of new fat and promoting the expression of genes related to cholesterol biosynthesis (36).

Of note, mechanistic studies have indicated that PRMT5 is involved in lipid metabolism reprogramming and tumor growth and metastasis through sirtuin 7 (SIRT7)-mediated deglycosylation of PRMT5 K387 (40). SIRT7 acts as an eraser for PRMT5 succinylation by mediating PRMT5 K387 deacetylation and inducing SREBP1a arginine methylation, promoting PRMT5-mep50 complex formation and increasing cholesterol, fatty acid and triglyceride biosynthesis in cells. PRMT5 regulates fatty acid metabolism and lipid droplet biosynthesis in white adipose tissue and realizes the reprogramming of lipid metabolism; a normal lipid metabolism is important for the regulation and abnormality of cholesterol metabolism (39).

In summary, as outlined in Fig. 1, PRMTs regulate ABC levels and RCT generation by mediating the expression of LXP and SREBP, controlling cholesterol excretion and degradation and participating in the dynamic balance of cholesterol regulation.

4. Relationship between PRMT family and AS

AS is the most common CVD and is characterized by the formation of AS or fibrous plaques in the vascular intima, which involves the large and middle arteries and leads to ischemic changes in the corresponding organs. Factors such as miRNAs, autophagy and epigenetic modifications may be associated with AS by affecting macrophage polarization (39). In recent years, numerous studies have indicated that PRMT2 and PRMT3 are closely associated with AS.

Relationship between PRMT2 and AS. After vascular injury factor intervention, PRMT2 knockout mice exhibited abnormal proliferation of vascular cells and intimal hyperplasia (41), leading to vascular endothelial dysfunction, which is a potential factor for AS. It has been reported that bone marrow-derived macrophages in mice lacking PRMT2 exhibit reduced cholesterol efflux, suggesting that PRMT2 is involved in the formation of foam cells and occurrence of AS (28). Li *et al* (23) indicated that overexpression of PRMT2 inhibited the formation of foam cells in RAW264.7 macrophages induced by ox-LDL. This mechanism may be related to an increase in ABCA1 expression and ABCA1-mediated cholesterol efflux.

Relationship between PRMT3 and AS. Chen *et al* (42) determined that the mRNA expression level of PRMT3 in the myocardial tissues of patients with AS was two-fold higher than that in healthy controls. The common carotid intima-media thickness is a measurement index of subclinical AS and variations in the PRMT3 gene are related to changes in this thickness (30). ADMA is a methylation-modified product of PRMT3. Doğan *et al* (43) indicated that ADMA is a potential factor for hypervolemia and AS in patients undergoing hemodialysis. These studies demonstrated that PRMT3 is closely related to AS by regulating the common carotid intima-media thickness and ADMA.

Small changes in plasma ADMA may cause large changes in cells, thereby altering the production of nitric oxide (NO) and leading to the development of CVDs (44). The impact of PRMT3 on AS may involve the following mechanisms: ADMA and ox-LDL molecules may inhibit NO production under the regulation of PRMT3, which is an important cause of AS. PRMT3 transfers a methyl group to arginine residues of histones and other proteins, resulting in asymmetric ADMA (30). ADMA is an endogenous competitive inhibitor of epidermal NO synthase and is a favorable predictor of CVD in patients with end-stage renal disease (45). Among patients with chronic kidney disease, the inhibitory effect of ADMA on NO synthesis is enhanced (46), which increases the risk of AS. In addition, ox-LDL molecules induce AS and enable monocytes to enter endothelial cells by binding to lectin-like ox-LDL receptor-1 (LOX-1), promoting foam cell formation and reducing intracellular NO concentrations (46).

PRMT3 is a cofactor for LXR transcription (31). As a transcription factor, LXR induces the expression of genes involved in cholesterol transport and efflux and prevents AS by promoting reverse cholesterol transport, reducing the accumulation of cholesterol in macrophages and preventing the formation of foam cells (28,47). Hoekstra *et al* (30) experimentally demonstrated that PRMT3 is an auxiliary activator that regulates the lipogenicity of LXR. Furthermore, PRMT3 may affect cholesterol metabolism and increase susceptibility to AS. The allosteric PRMT3 inhibitor SGC707 did not alter the susceptibility to AS, but SGC707 may affect the ADMA/NO system, revealing a correlation between PRMT3 and AS.

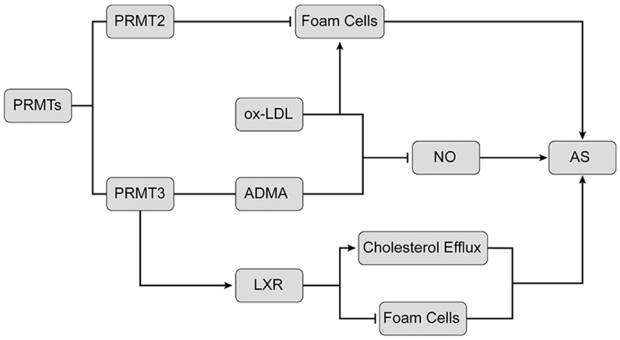

Figure 2. Relationship between the family of PRMTs and AS. Overexpression of PRMT2 inhibits the formation of foam cells induced by ox-LDL. ADMA is a methylation modification product of PRMT3. AMDA and ox-LDL inhibit NO production, leading to AS. PRMT3 is a special cofactor for LXR transcription. LXR induces the expression of genes involved in cholesterol transport, reducing the accumulation of cholesterol in macrophages and preventing the formation of foam cells. AS, atherosclerosis; NO, nitric oxide; ADMA, asymmetric dimethyl-arginine; PRMT2, protein arginine methyltransferase 2; ox-LDL, oxidized low-density lipoprotein; LXR, liver X receptor.

In summary, as illustrated in Fig. 2, PRMT2 inhibits ox-LDL-induced foam cell formation. PRMT3 is closely related to AS by regulating the expression of arginine methylation products and LOX-1.

5. PRMTs and heart failure

Heart failure is the leading cause of hospitalization and death among the elderly worldwide (48). Heart failure is a chronic disease that generally starts with ventricular hypertrophy and its main feature is an increase in cell size associated with increased ventricular remodeling and fibrosis. In the chapter below, the role of PRMTs in the pathogenesis of heart failure is introduced.

PRMT1 and heart failure. PRMTs are overexpressed in numerous types of cancer (4); however, the role of PRMTs in heart disease has remained largely elusive. It has been indicated that calmodulin-dependent protein kinase II (CaMKII) disorder is closely related to myocardial hypertrophy and heart failure. However, the mechanisms regulating CaMKII activity are not fully understood (49). PRMT1 is essential for preventing excessive activation of CaMKII in the heart. For instance, cardiac PRMT1-negative mice rapidly developed dilated cardiomyopathy (DCM) and heart failure within two months, accompanied by cardiomyocyte hypertrophy and fibrosis. In isolated cardiomyocytes, loss of PRMT1 may cause a hypertrophic response with increased expression of remodeling genes. In the heart or cardiomyocytes deficient in PRMT1, the level of active CaMKII was significantly increased. PRMT1 interacts with and methylates CaMKII at

arginine residues 9 and 275, resulting in CaMKII inhibition. Pharmacological inhibition of CaMKII restores contractile function in PRMT1-deficient mice (49). Therefore, PRMT1 deactivates CaMKII and maintains normal heart function, which is important for developing drugs to treat heart failure.

In addition, PRMT1 may regulate slow delayed rectifier potassium current (IKs) activity by regulating the affinity of phosphatidylinositol 4,5-bisphosphate (PIP2), a membrane lipid of the IKs channel. IKs, assembled by the pore-forming KCNQ1α subunit and the auxiliary KCN1β subunit, is crucial for the late repolarization of cardiac action potentials. The activity of IKs may be modulated by the regulation of PIP2 availability or PIP2 affinity of IKs. The combination of PIP2 and KCNQ1 may serve to stabilize the channel in the open state. PRMT1 may regulate the IKs channel function by inducing arginine methylation of the KCNQ1 subunit in the IKs channel. Studies on the recombinant IKs channel have shown that in 293T cells containing human KCNQ1 subunits, inhibition of PRMT1 reduces the methylation of KCNQ1, thereby reducing the binding of PIP2 to KCNQ1 and inducing a decrease in IKs activity. This indicates that PRMT1 is necessary for the binding of KCNQ1 to PIP2. Recombinant IKs channel studies have indicated that inhibition of PRMT1 reduces the methylation of KCNQ1 in 293T cells containing human KCNQ1 and KCNE1 subunits, thereby reducing the binding of PIP2 to KCNQ1 and inducing a decrease in IKs (50). The PRMT1 function is necessary for the channel to be combined with PIP2. Inhibition of PRMT1 prolonged the duration of ventricular action potentials by reducing IKs. PRMT1-mediated regulation of cardiac IKS activity may be a key target for preventing excessive prolongation of the time course and arrhythmias in patients with heart failure (50).

PRMT4 and heart failure. PRMT4 is a type I protein arginine methyltransferase involved in a variety of cell biological processes. Myocardial infarction is caused by irreversible myocardial necrosis induced by a sharp decrease in blood flow to a certain area of the heart. Heart remodeling after myocardial infarction eventually leads to heart failure. Previous studies have mostly focused on the involvement of PRMT4 in the occurrence and development of various tumors, but its role in cardiomyocytes remains unclear. PRMT4 expression is significantly reduced in the ischemic myocardium and hypoxic cardiomyocytes, and overexpression of PRMT4 aggravates cardiac remodeling after myocardial infarction (51). PRMT4 overexpression promotes hypoxia-induced cardiomyocyte apoptosis, whereas inhibition of PRMT4 expression allows cardiomyocytes to avoid apoptosis by regulating the apoptosis-related protein Bax (52). It was also indicated that loss of PRMT4 increased Notch1-mediated podocyte apoptosis through the PRMT4-protein kinase AMP-activated catalytic subunit α1-Notch1-CB1R signaling axis (52). In summary, hypoxia-induced upregulation of PRMT4 promotes cardiomyocyte apoptosis and aggravates cardiac remodeling after myocardial infarction. However, the precise underlying mechanisms require further investigation. Of note, this discovery may provide new ideas for the treatment of myocardial infarction by inhibiting PRMT4 expression.

In Fig. 3, the role of PRMTs in heart failure is summarized. PRMT1 maintains the normal function of the heart by inactivating CaMKII. Hypoxia-induced PRMT4 overexpression upregulates cardiomyocyte apoptosis, whereas the following PRMT5 interacts with GATA4 to inhibit its role in promoting hypertrophy gene expression, leading to heart failure.

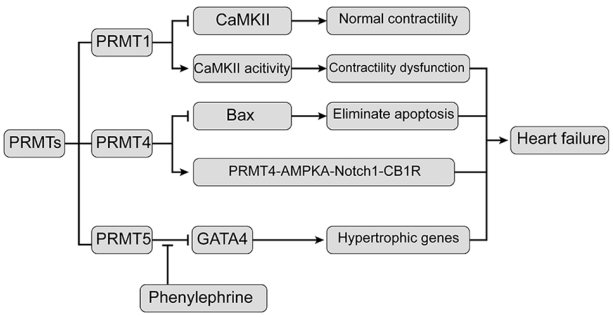

Figure 3. Relationship between PRMTs and heart failure. PRMT1 interacts with and methylates CaMKII at arginine residues 9 and 275, resulting in inhibition of CaMKII. Inhibition of PRMT4 expression allows cardiomyocytes to eliminate apoptosis by regulating the apoptosis-related protein Bax. PRMT4 increases Notch1-mediated podocyte apoptosis through the PRMT4-AMPKa-Notch1-CB1R signaling axis. PRMT5 leads to methylation of arginine at sites 229, 265 and 317 of GATA4, resulting in inhibition of transcriptional activity of GATA4. In addition, PRMT5 is transferred from the nucleus to the cytoplasm under phenylepinephrine stimulation. In this way, PRMT5 reduces the inhibition of GATA4 activity in the nucleus and leads to the expression of hypertrophic genes in the cardiomyocytes. At last, these above mechanisms lead to heart failure. CAMKII, calmodulin-dependent protein kinase II; PRMT1, protein arginine methyltransferase 1; AMPKa, protein kinase AMP-activated catalytic subunit α1; GATA4, GATA binding protein 4.

PRMT5 and heart failure. DCM is a complex myocardial disease characterized by left ventricular dilatation and systolic dysfunction, and it usually affects middle-aged males. Its occurrence is related to viral infection, family inheritance and cellular immunity. The main symptom of DCM is congestive heart failure.

Cardiac protein O-GlcNAcylation, as a key enzyme for dynamic regulation, has been detected in various cardiac diseases. Studies suggested that O-GlcNAcylation has an important physiological role in maintaining cardiac function and O-GlcNAcylation dysregulation has been indicated to be closely related to cardiac disease. Overexpression of O-GlcNAcylation contributes to DCM formation and premature death (53). Reducing elevated O-GlcNAcylation may be a potential treatment for human DCM.

As a novel protein O-GlcNAcylation regulator, PRMT5 mainly regulates O-GlcNAcylation by regulating the alternative splicing of O-GlcNAcase mRNA, symmetrically dimethylating downstream targets including RNA splicing proteins (34). Mechanistic studies have indicated that PRMT5 is able to prevent DCM by inhibiting protein O-GlcN acylation (53). In human DCM samples, PRMT5 expression was significantly downregulated (36). The absence of PRMT5 causes abnormal increases in myocardial O-GlcNAcylation levels, aggravates myocardial injury and further reduces the ejection fraction and systolic function, leading to cardiac dysfunction and triggers DCM.

There is a further mechanism leading to DCM. N^6-methyladenosine (m^6A) is the most abundant internal

epigenetic modification on eukaryotic mRNAs (54). As the sole nuclear m^{6}A reader, YTH domain containing 1 (YTHDC1) may be related to DCM. Mice with YTHDC1 deficiency developed obvious left ventricular chamber enlargement and severe systolic dysfunction, which are typical manifestations of DCM (55). Titin is a sarcomeric protein that determines the structure and biomechanical properties of striated muscle and its defect is directly associated with DCM (56). According to a study by Gao *et al* (55), Titin is the direct target of YTHDC1 and knockout of YTHDC1 in heart resulted in abnormal splicing of Titin, contributing to disarray of sarcomere structures in the cardiomyocytes, which is a typical feature of DCM. To conclude, depletion of YTHDC1 induces DCM by abnormal splicing of Titin and DCM is a common cause of heart failure (55). However, whether PRMTs are involved in the regulation of YTHDC1 depletion remains elusive and further research is anticipated to explore this novel mechanism.

6. PRMTs and myocardial hypertrophy

PRMT5 and cardiac hypertrophy. PRMT5 is a protein arginine methyltransferase that catalyzes the symmetric dimethylation of arginine residues on the target protein. It participates in numerous important cellular processes, ranging from gene expression regulation to cell proliferation and differentiation. PRMT5 is highly expressed in the heart; however, its functional role in the heart remains elusive. Among the six GATA transcription factors in vertebrates, GATA4-6 are expressed in the heart and regulate the expression of numerous heart-specific genes, such as β-myosin heavy chain, cardiac troponin C, cardiac troponin I, atrial natriuretic peptide and brain natriuretic peptide (57,58). GATA4 is important for promoting the development of cardiac hypertrophy. For instance, overexpression of GATA4 induces cardiomyocyte hypertrophy in cultured cardiomyocytes and mouse hearts (59), whereas inhibiting the activity of GATA4 results in the suppression of hypertrophic gene expression in cardiomyocytes (60). PRMT5 specifically interacts with GATA4 in cardiomyocytes. This interaction leads to methylation of arginine at positions 229, 265 and 317 of GATA4 to result in inhibition of the transcriptional activity of GATA4. In addition, PRMT5 was indicated to be transferred from the nucleus to the cytoplasm in response to phenylephrine stimulation. Thus, the absence of PRMT5 decreases inhibition of GATA4 activity in the nucleus, leading to the expression of cardiomyocyte mast genes (61). These findings indicate that PRMT5 is an important regulator of cardiac hypertrophy signaling and suggest that strategies aimed at activating PRMT5 in the heart are useful for preventing cardiac hypertrophy and heart failure (62).

PRMT6 and cardiac hypertrophy. PRMT6 is the main methyltransferase that acts on asymmetric dimethylation of histone H3 at arginine 2 (H3R2Me2a) (63). Researchers have evaluated the expression of PRMTs in the left ventricle of failing and control hearts. The results indicated that in failing human hearts, PRMT6 was significantly upregulated compared with that in control hearts, which also occurs in the early stages of cardiac hypertrophy in mouse hearts undergoing pressure-overload hypertrophy induced by coarctation of transverse aortic constriction and in neonatal rat ventricular myocytes stimulated with the hypertrophy agonist phenylephrine (64). These changes are related to the significant increase in H3R2Me2a and a decrease in trimethylation of lysine 4 on histone H3 in neonatal rat ventricular myocytes and *in vivo* (65). Of note, overexpression of PRMT6 in neonatal rat ventricular myocytes enhanced the expression of the hypertrophy marker atrial natriuretic peptide. By contrast, silencing of PRMT6 reduced the expression of atrial natriuretic peptide and the cell size, indicating that PRMT6 is essential for the phenylephrine-mediated hypertrophy response (64). Therefore, PRMT6 is a key regulator of myocardial hypertrophy, suggesting that H3R2Me2a is an important histone modification and that PRMT6 mediates myocardial hypertrophy through differential regulation of histone H3 arginine methylation.

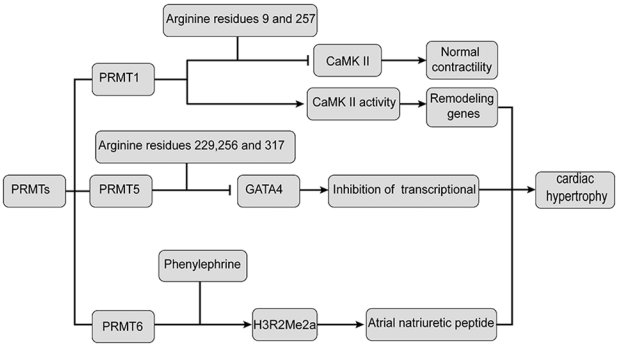

Figure 4. Relationship between PRMTs and cardiac hypertrophy. PRMT1 interacts with CaMKII and is methylated at arginine residues 9 and 275, leading to inhibition of CaMKII, which may lead to hypertrophic gene expression. PRMT5 interacts with GATA4, resulting in methylation at sites 229, 265 and 317 of GATA4 arginine residues, thereby inhibiting the transcriptional activity of GATA4, which may lead to the expression of hypertrophic genes. PRMT6 mediates cardiac hypertrophy through differential regulation of phenylephrine and asymmetric dimethylation of H3R2Me2a. CAMKII, calmodulin-dependent protein kinase II; PRMT1, protein arginine methyltransferase 1; AMPKa, protein kinase AMP-activated catalytic subunit α1; GATA4, GATA binding protein 4; H3R2Me2a, histone H3 at arginine 2.

In Fig. 4, the role of PRMTs in cardiac hypertrophy is illustrated. PRMT1 and PRMT6 are involved in the mediation of cardiac hypertrophy, while PRMT5 reduces the inhibition of GATA4 activity and leads to the expression of hypertrophic genes in cardiomyocytes.

PRMT7 and cardiac hypertrophy. PRMT7 is a type III enzyme that catalyzes monomethylation. PRMT7 is associated with biological processes, such as regulating the proliferation of renal cell carcinoma by regulating β-catenin activity (66). Mechanistic studies revealed that PRMT7 suppresses the Wnt/β-catenin signaling pathway by methylation of β-catenin at arginine residue 93, which is critical for the regulation of β-catenin activity in the control of cardiac hypertrophy and fibrosis (67).

Accumulating evidence suggests a prominent role of Wnt/β-catenin signaling in cardiac hypertrophy and myocardial fibrosis. The importance of Wnt/β-catenin signaling in cardiomyopathy is underscored by the fact that inhibition of Wnt/β-catenin signaling inhibits cardiac remodeling, post-infarction mortality and decreased cardiac function (68). Wnt/β-catenin signaling is regulated at multiple levels through complex mechanisms (69). Upon binding of Wnt/β-catenin

ligands to frizzled receptor and co-receptor lipoprotein receptor-related protein 5/6, a signaling cascade is initiated to activate β-catenin by suppression of inhibitory phosphorylation, ubiquitination and proteasomal degradation, resulting in stabilization and subsequent nuclear translocation of β-catenin and induction of target gene expression (70). Although the precise regulation of β-catenin activity appears to be essential for normal cardiac remodeling, the mechanism of β-catenin inhibition is currently unknown.

7. Differences between PRMT1-PRMT6 in CVD and their application in CVD treatment

In the above chapters, the link between PRMT1-PRMT6 and CVD was described. PRMT1 and PRMT2 are cardioprotective enzymes. PRMT1 depletion leads to myocardial hypertrophy and heart failure by creating an imbalance of CaMKII (49). In addition, PRMT1-mediated regulation of cardiac IKs activity may be a target for preventing excessive prolongation of the course of disease and arrhythmia in patients with heart failure (50). PRMT2 upregulates the expression of ABCA1 protein, inhibits foam cell formation and resists AS, while ABCA1 mediates cholesterol efflux (28). PRMT3-PRMT6 promote the occurrence and development of heart disease. As a nuclear cofactor, PRMT3 regulates LXR lipogenesis by upregulating the expression of ABCA1 and ABCG1, thereby increasing the expression of lipogenic proteins, resulting in systemic cholesterol accumulation and increasing the susceptibility to AS (30,31,33). PRMT4 is involved in myocardial infarction and its overexpression promotes hypoxia-induced cardiomyocyte apoptosis by regulating the apoptosis-related protein Bax (51,52). PRMT5 and PRMT6 are involved in the occurrence of myocardial hypertrophy. PRMT5 increases the synthesis of fat by enhancing the stability of SREBP1 (36,39); At the same time, PRMT5 also prevents myocardial hypertrophy and DCM by inhibiting the effect of GATA4 and inhibiting protein O-GlcN acylation (53,59,61), respectively. Silencing of PRMT6 expression inhibits the hypertrophy-promoting effect of phenylephrine and participates in the formation of cardiac hypertrophy (64). PRMT7 inhibits cardiac remodeling, post-infarction mortality and decreased cardiac function by inhibiting the Wnt/β-catenin signaling pathway (67,68). Therefore, increasing the activity of PRMT1 and PRMT2 or decreasing the expression of PRMT3-PRMT6 may be potential therapeutic targets for CVDs.

8. Conclusion

PRMT1-7 is involved in the occurrence of numerous CVDs, such as AS, heart failure and myocardial hypertrophy, by regulating the methylation of arginine residues, the activity of LXR transcription factors and signal transduction enzymes. Other PRMTs, such as PRMT8 and -9, have not been demonstrated to have a role in CVD and require further analysis. The present study mainly introduced the role of PRMT2, -3 and -5 in cholesterol metabolism and reviewed the relationship between PRMT1 and maintenance of normal cardiac function between PRMT4 and myocardial infarction, between PRMT5-7 and myocardial hypertrophy, and between PRMT2 and -3 and AS in vascular diseases. As an epigenetic species, the differential expression of PRMT1-PRMT7 and their mediating roles in CVD are complex, involving both enzyme activity-dependent and possibly non-enzyme activity-dependent effects. Different ways of action may be the reason why they have different roles in CVDs.

Although the role of PRMTs in CVD has been examined, numerous issues remain to be addressed, such as how PRMT2 upregulates the expression of ABCA1 and the detailed underlying mechanism. Furthermore, whether cardiovascular-related inhibitors of PRMTs affect other organs remains elusive. In addition, PRMTs may also affect the occurrence and development of CVDs in manners that have not been identified. Further studies of PRMTs will reveal their roles and mechanisms in CVDs, leading to the identification of drug targets and improving their clinical applications.

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Availability of data and materials

Not applicable.

Authors' contributions

SiZ and CZ were involved in the conception and design of this study. AH and FH performed the literature search selection. AM and ShZ contributed to manuscript revision. ZW coordinated the study and reviewed the manuscript. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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