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Functional Roles of Protein Arginine Methyltransferase 5 in Cardiovascular Diseases

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Abstract

Protein arginine methyltransferase 5 (PRMT5) is a protein arginine methyl transferase that catalyzes the symmetrical dimethylation of arginine residues within target proteins. PRMT5 is shown to associate with and methylate histone or non-histone proteins in cells, and plays key roles in cell development, survival and apoptosis. In this review, the current state of knowledge and functional roles of PRMT5 in vascular systems are discussed.

Keywords: PRMTs; Arginine methylation; Cardiovascular diseases

Introduction

Post-translational modification of proteins, such as phosphorylation, methylation, ubiquitylation and sumoylation, is observed in all known living organisms and plays key regulatory roles in cell development, survival and apoptosis [1-3]. Among these protein post-translational modifications, protein methylation is one of the most abundant modifications. For example, Boffa et al. found that about 2% of arginine residues were found to be dimethylated in total protein extracts from rat liver nuclei [4]. In this regarding, methylation was occurred at nitrogen of the terminal guanidine of arginines catalyzing by protein arginine methyltransferases (PRMTs), which transfer methyl groups from the S-adenosyl methionine methyl donor to specific methyl acceptors [5]. To date, 11 protein arginine methyltransferases have been found and were classified into two types (I-II) based on the types of methylarginine products they produce. Type I includes PRMT1, PRMT2, PRMT3, PRMT4, PRMT6 and PRMT8, and type I enzymes form monomethylarginine and asymmetric dimethylarginine. However, Type II enzymes form monomethylarginine and symmetric dimethylarginine (these enzymes including PRMT5, PRMT7, PRMT9, PRMT10 and PRMT11) [6]. Here, we provide a briefly introduction to PRMT5 and discuss the current state of knowledge regarding the functions of this protein in vascular systems.

Substrates and Function of PRMT5

It has been realized that most PRMTs methylate arginine residues localized within glycine and arginine-rich (GAR) sequences. However, PRMT5 methylates both GAR and non-GAR motifs in target proteins [5]. In general, the substrates of PRMT5 could be divided into histone and non-histone proteins, and thus exerting diverse biological functional roles, including transcriptional regulation, cell cycle progression [7], RNA metabolism [8], and ribosome biogenesis [9]. In mammalian cells PRMT5 has been shown to localize in both nucleus and cytoplasm. In the nucleus, PRMT5 has been found in the SWI/SNF and NURD chromatin-remodeling complexes where it methylates histones as well as transcription factors, which results in a transcriptional repression. For example, Kwak et al. reported that PRMT5 acts as a transcriptional repressor by methylating histones H3 and H4 and transcriptional elongation factor SPT5 [10]. Recently, PRMT5 was shown to methylate histone H2AR3 in the cytoplasm of mouse embryonic stem cells [11]. In the cytoplasm, PRMT5 forms a 20 S protein arginine methyltransferase complex consisting of spliceosomal snRNP Sm proteins, PRMT5, pICln, and WD repeat protein (MEP50/WD45), which is essentially involved in pre-mRNA splicing [12]. Interestingly, PRMT5 has been shown to exert different or even opposite effects due to its different cellular localization, and thus make the function of PRMT5 complicate. For example, in cytoplasm PRMT5 is required for the growth of prostate cancer cells in a methyltransferase-dependent manner, whereas PRMT5 in the nucleus inhibits prostate cancer cell growth [13]. We also show that PRMT5 is highly expressed and localized in nucleus in cardiomyocytes. PE could induce the translocation of PRMT5 from nucleus to cytoplasm in cardiomyocytes, and thus resulted in cardiac hypertrophy. However, overexpression of PRMT5 by infected PRMT5 bearing adenovirus could significantly attenuate PE-induced cardiac hypertrophy [14]. In this regards, the mechanism how PRMT5 cellular transferred is remain unknown.

Recently, non-histone protein which could be methylated has been wildly reported. For example, proteins like p53, ASK1, GATA4, HOXA9 and NF-κB, have been reported to be methylated by PRMT5, and implicated in the regulation of cell growth, apoptosis, and inflammation [14-18]. Jansson et al. reported that PRMT5 is a cofactor for p53. When DNA is damaged, PRMT5 was recruited to p53, which allowing PRMT5 to methylate p53 at Arg 333, Arg 335 and Arg 337 [15]. While, Wei et al. reported that PRMT5 regulates NF-κB by dimethylating R30 of the p65 subunit, and subsequently activates NF-κB [18].

Interestingly, the crosstalk between methylation and other kind of post-translational modifications in target proteins has been observed

by our group and others. Hung group reported that epidermal growth factor receptor (EGFR) is methylated at Arg1175 by PRMT5, and then Arg1175 methylation positively modulates EGF-induced EGFR trans-autophosphorylation at Tyr1173 [19]. p300 has been shown to interact with GATA4 and potentiate its transcriptional activity through acetylation, our group found that the methylation of GATA4 by PRMT5 in cardiomyocytes attenuates the interaction of GATA4 and p300, thus potential the aceacetylation of GATA4, which leads to an inhibition of GATA4 transcriptional activity and cardiomyocyte hypertrophy [14].

PRMT5 in Cardiovascular System

It has been reported that type 1 PRMTs are expressed in the heart, smooth muscle cells, and endothelial cells, however, the expression pattern has not been documented in detail. The effect of asymmetric dimethylarginine (ADMA) and L-NMMA (which are synthesized when arginine residues in proteins are methylated by the action of PRMTs) on cardiovascular system had been documented in many references [20-22]. For example, ADMA inhibits eNOS activity, and it elevates blood pressure, causes vasoconstriction, impairs endothelium-dependent relaxation, and increases endothelial cell adhesiveness [21,23]. Elevated ADMA levels also have been found in animal models of type 1 and type 2 diabetes and in patients with overt type 2 diabetes, which further indicted the potential roles of PRMTs in cardiovascular diseases [24]. As mentioned above, protein arginine methyltransferase 5, a protein arginine methyltransferase that catalyzes the symmetrical dimethylation of arginine residues within target proteins, has been implicated in many essential cellular processes ranging from the regulation of gene expression to cell proliferation and differentiation [3]. It has been found that PRMT5 is widely expressed in different human tissues [25]. Importantly, high expression of PRMT5 is observed in heart, skeletal muscle, and testis. Interestingly, the expression of PRMT5 in the heart is substantially reduced in aged rats, thus implicating a potential role of PRMT5 in age-related heart diseases, such as cardiac hypertrophy and heart failure [25]. Furthermore, Tee et al. reported that loss of PRMT5 results in early embryonic lethality in mice [11], further indicated the important role of PRMT5 in mice development.

NR4A receptors are immediate-early genes that are regulated by various physiological stimuli and are involved in a wide array of important biological processes. Recently, there has been much attention paid to the function of these receptors in cardiovascular system [26-28]. For example, our recent study has implicated Nur77 as a regulator for the expression of ET-1 in ECs [29]. Recently we have expanded our research to explore the functional role of Nur77 in cardiomyocytes. Our preliminary data indicated Nur77 attenuates ISO-Induced cardiac hypertrophy *in vitro* and *in vivo* [30]. Furthermore, we identified PRMT5 as Nur77 associated proteins in NRVMs, and ISO stimuli could interrupt the interaction of Nur77 and PRMT5 (data not shown), suggesting that PRMT5 may be involved in cardiovascular system via the functional regulating of Nur77. In addition, PRMT5 was reported to involved in sustain adult hematopoiesis. Using PRMT5 conditional KO mice, Liu et al. demonstrated that contribution of PRMT5 to adult hematopoiesis. They found that Loss of PRMT5 triggered an initial but transient expansion of hematopoietic stem cells (HSCs). However, PRMT5 deletion resulted in a concurrent loss of hematopoietic progenitor cells (HPCs), leading to fatal bone marrow (BM aplasia). Moreover, PRMT5-specific effects on hematopoiesis were cell intrinsic and depended on PRMT5 methyltransferase activity [31].

Recently, our previous results also show that PRMT5 is highly expressed in cardiomyoctes and methylates GATA4 in hypertrophy cardiomyoctes [14]. Interestingly, the intermediary species L-NMMA, which is produced by PRMT5, is eNOS inhibiter, further implicates the potential roles of PRMT5 in cardiovascular diseases [32]. PRMT5 is also highly expressed in the vascular cells. For example, Bandyopadhyay et al. reported that PRMT5 is required for HOXA9 mediated VCAM-1 expression in endothelial cells [17]. We also have elucidated a mechanism that PRMT5 regulates H_2O_2 induced endothelial cell apoptosis via methylating ASK1 [16]. Together, PRMT5 is highly expressed in cardiovascular tissues and cells, however, the functional roles of this protein need more elucidated, and these work are ongoing in our lab.

Concluding Remarks

In recent years, significant progress has been made in understanding the methylation in mammalian cells. Other's and our data support PRMT5 as an important regulator in cardiovascular system by interacting and methylating histone and non-histone target proteins. Cardiovascular disease is remarkably age-relative, while the age-relative change in methylation was shown not only in a genome-wide but also in protein level. Considering the fact that the expression of PRMT5 in the heart is substantially reduced in aged rats, thus further investigation of the function of PRMT5 will give us new insight to discovery and development a potential therapeutic approach for the prevention of cardiovascular diseases.

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Competing interests

The authors declare that they have no conflicts of interest with the contents of this article.

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