


Review

Structure, Activity and Function of the Protein Arginine Methyltransferase 6

Somlee Gupta ¹, Rajashekar Varma Kadumuri ², Anjali Kumari Singh ², Sreenivas Chavali ² 
and Arunkumar Dhayalan ^{1,*}

¹ Department of Biotechnology, Pondicherry University, Puducherry 605014, India; somleegupta@gmail.com

² Department of Biology, Indian Institute of Science Education and Research (IISER) Tirupati, Tirupati 517507, India; rajashekar@labs.iisertirupati.ac.in (R.V.K.);

anjalisingh@students.iisertirupati.ac.in (A.K.S.); schavali@iisertirupati.ac.in (S.C.)

* Correspondence: arun.dbt@pondiuni.edu.in; Tel.: +91-413-2654789

Abstract: Members of the protein arginine methyltransferase (PRMT) family methylate the arginine residue(s) of several proteins and regulate a broad spectrum of cellular functions. Protein arginine methyltransferase 6 (PRMT6) is a type I PRMT that asymmetrically dimethylates the arginine residues of numerous substrate proteins. PRMT6 introduces asymmetric dimethylation modification in the histone 3 at arginine 2 (H3R2me2a) and facilitates epigenetic regulation of global gene expression. In addition to histones, PRMT6 methylates a wide range of cellular proteins and regulates their functions. Here, we discuss (i) the biochemical aspects of enzyme kinetics, (ii) the structural features of PRMT6 and (iii) the diverse functional outcomes of PRMT6 mediated arginine methylation. Finally, we highlight how dysregulation of PRMT6 is implicated in various types of cancers and response to viral infections.

Keywords: protein arginine methylation; PRMT6; post-translational modification; H3R2me2a; epigenetics; cancer



Citation: Gupta, S.; Kadumuri, R.V.; Singh, A.K.; Chavali, S.; Dhayalan, A. Structure, Activity and Function of the Protein Arginine Methyltransferase 6. *Life* **2021**, *11*, 951. <https://doi.org/10.3390/life11090951>

Academic Editor: Nikolaos Labrou

Received: 26 August 2021

Accepted: 8 September 2021

Published: 11 September 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Protein arginine methyltransferases (PRMTs) are the family of enzymes which methylate the arginine residue(s) of substrate proteins and regulate a wide range of cellular events including transcription, splicing, translation, DNA damage responses and phase separation [1]. PRMTs are classified into three types depending on the nature of the methylarginine that they form. Type I PRMTs (PRMT1, PRMT2, PRMT3, PRMT4, PRMT6 and PRMT8) and Type II PRMTs (PRMT5 and PRMT9) generate asymmetric dimethylarginine and symmetric dimethylarginine, respectively, in addition to the monomethylarginine. Type III enzyme (PRMT7) exclusively generates monomethylarginines in proteins [2,3].

Protein arginine methyltransferase 6 (PRMT6) is a type I PRMT which is involved in epigenetic regulation of gene expression [4–6], alternative splicing [7,8], development and differentiation [9–13], DNA repair [14], cell proliferation and senescence [15–20], DNA methylation [21], mitosis [22,23], inflammation [24–26], innate antiviral immunity [27], spermatogenesis [28], transactivation of nuclear receptors [7,29,30] and cell signaling [31,32]. A high throughput yeast two-hybrid screening of PRMT6 identified 36 proteins as potential interaction partners of PRMT6 suggesting the role of PRMT6 in various additional, so far unidentified cellular functions [33]. In addition to these physiological functions, the dysregulation of PRMT6 is implicated in viral diseases [34–41], cancers [42] and cardiac hypertrophy [43].

The human PRMT6 gene, located on Chromosome 1, encodes for the 41.9 kDa PRMT6 enzyme. PRMT6 is predominantly localized to the nucleus, in stark contrast to PRMT3 and PRMT5 which are preponderantly cytosolic, while other PRMTs are found in both nucleus and cytosol [44]. PRMT6 is expressed in a wide range of tissues with high expression in

kidney and testes [44]. The F-box proteins, FBXO24 and FBXW17, regulate the protein levels of PRMT6 by facilitating its proteasomal degradation [45,46]. PRMT6 generates asymmetric dimethylation modifications in histone 3 at arginine 2, arginine 17 and arginine 42 (H3R2me2a, H3R17me2a and H3R42me2a) [4–6,47,48] and in histone H2A at arginine 26 (H2AR26me2a) [49] and participates in the epigenetic regulation of gene expression. In addition to the histones, PRMT6 methylates a wide range of non-histone proteins and regulates various biological functions. In the following sections, we discuss the biochemical features, structural aspects, epigenetic functions of PRMT6, functional outcomes of PRMT6-mediated methylation of non-histone substrates and viral proteins and the role of PRMT6 in various types of cancers.

2. Biochemical Features

PRMT6 was identified as a protein arginine methyltransferase based on the presence of conserved catalytic core of PRMT family members. *In vitro* studies using the GST-GAR substrate, showed that the recombinant PRMT6 enzyme generates monomethylarginines and asymmetric dimethylarginines, establishing PRMT6 as a bona fide type I PRMT enzyme [44]. GST-GAR, an *in vitro* substrate used to investigate the enzymatic activity of PRMTs, is a GST fusion of N-terminal region of the human rRNA 2'-O-methyltransferase fibrillarin enzyme (amino acids 1 to 148). GST-GAR contains nine arginine residues in the sequence context of "RGG" and six arginine residues in the sequence context "RG" [50–52].

Kinetic studies of PRMT6 mediated methylation of GST-GAR substrate revealed that it generates asymmetric dimethylarginines in a processive manner [44]. Furthermore, investigation of kinetics of recombinant PRMT6 with substrate peptides containing a single arginine or monomethylarginine residue [53] revealed that PRMT6 follows an ordered sequential mechanism of catalysis in which the S-adenosyl-L-methionine (SAM) binds to the enzyme first, followed by the binding of the substrate peptide resulting in the formation of a ternary complex (Figure 1A) [53,54]. Consequent to the methyl group transfer, the methylated substrate peptide dissociates first from the enzyme followed by the S-adenosyl-L-homocysteine (SAH) [53,54]. The catalytic efficiency of PRMT6 on the monomethylarginine containing substrate peptides is much higher than that of the substrate peptides with unmethylated arginine [53]. Notably, peptide products with asymmetric dimethylarginine could not be detected in the enzymatic reaction of PRMT6 with unmethylated arginine containing peptides. Collectively these findings suggest that the PRMT6 enzyme generates asymmetric dimethylarginine in a distributive manner rather than introducing two methyl groups processively in a single arginine residue in a single binding event [53].

However, this ordered sequential kinetic mechanism of PRMT6 enzyme was contradicted by a subsequent study which showed that the pre-incubation of SAM with the PRMT6 enzyme did not alter the IC₅₀ of C21 peptide on the activity of PRMT6 [55]. C21 is a modified H4 tail peptide which contains chloroacetamide modified ornithine at arginine 3 position and this C21 peptide inhibits the enzymatic activity of PRMTs irreversibly with high selectivity for PRMT1 and modest selectivity for PRMT6 [55,56]. This suggests that the binding of the SAM with the enzyme is not a pre-requisite step for the substrate peptide binding, challenging the ordered sequential kinetic mechanism of PRMT6 [55]. This observation prompted further detailed investigations of the kinetic mechanism of PRMT6 catalysis. Product inhibition studies and usage of dead-end analogs revealed that PRMT6 follows a rapid equilibrium and random kinetic mechanism with the generation of dead-end complexes (Figure 1B) [55]. These studies led to the proposal that PRMT6 binds to the substrate peptides and SAM in a random fashion to produce a ternary complex and products dissociate randomly after the methyl group transfer to generate the free enzyme [55]. This necessitates detailed structural studies of PRMT6 in complex with the proper substrate peptide and thorough kinetic studies to resolve this conflict and delineate the actual kinetic mechanism of PRMT6 catalysis.

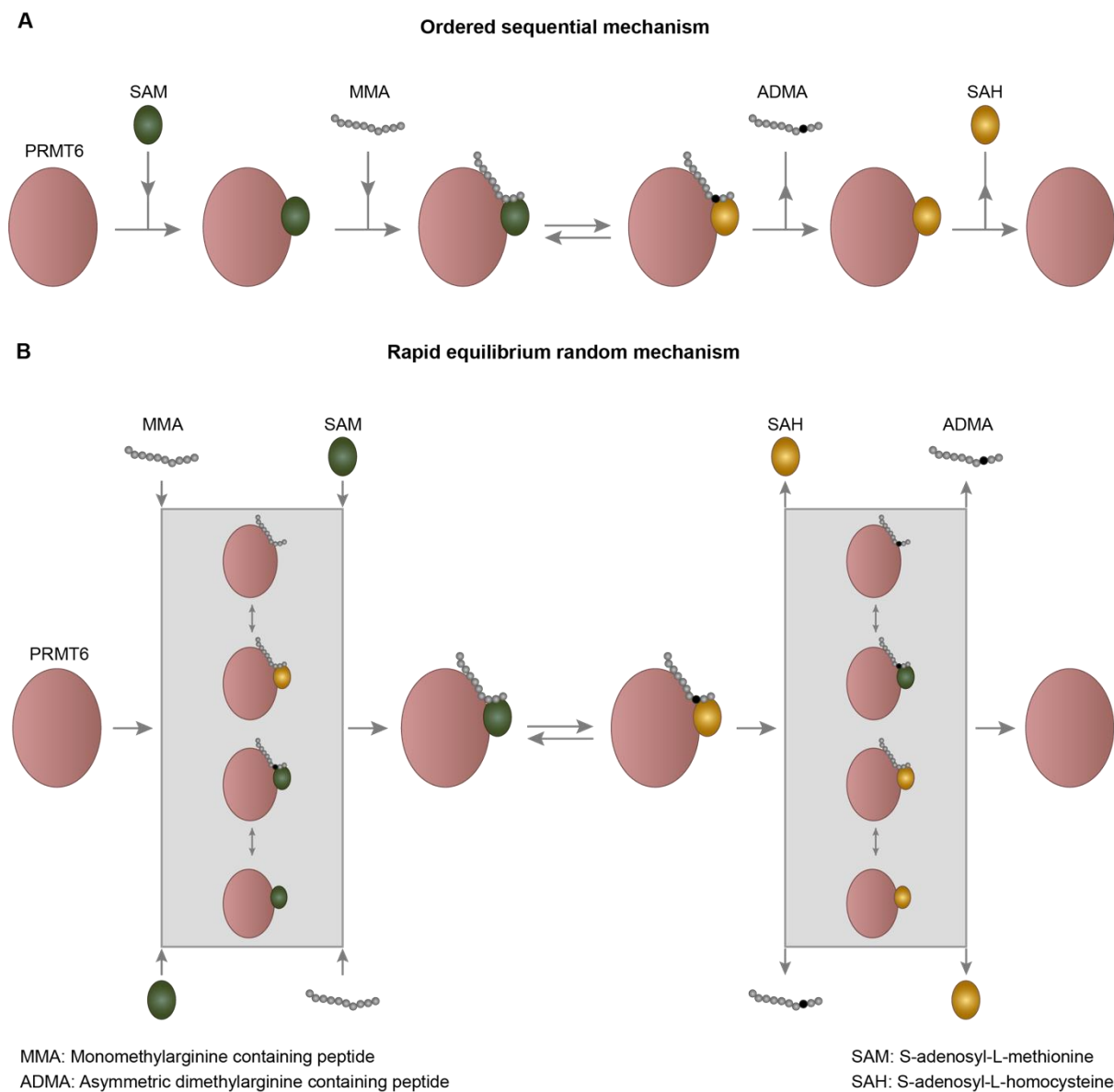


Figure 1. The proposed kinetic mechanisms of PRMT6 catalysis. Schematic representation of (A) Sequential ordered kinetic mechanism and (B) Rapid equilibrium random mechanism with dead-end complexes.

In addition to methylating its substrates, PRMT6 also undergoes automethylation at Arg35. This automethylation of PRMT6 regulates its stability and anti-HIV1 function without affecting its catalytic activity [44,57]. High throughput mass spectrometry analysis of PRMT6 activity on the H3 peptides carrying different amino acid exchanges at different positions showed that PRMT6 is relatively a non-specific enzyme *in vitro* as it tolerated most of the amino acid substitutions, with preference for positively charged amino acids and bulkier amino acids around the target arginine. PRMT6 exhibits a higher preference to methylate RG or RGK motif containing peptides more efficiently than the RGG motif containing peptides *in vitro* [58]. Contrarily, there is a higher preference of PRMT1 to methylate RGG motif containing substrates, while PRMT4 shows a preference to methylate the substrates in which the target arginine is flanked by the proline residues [58–61].

Given that the PRMT6 exhibits a relaxed substrate specificity, it is highly likely that it might methylate several hitherto unidentified substrate proteins, including the substrates of other PRMTs. Indeed, an *in vitro* methylation assay on rat cell extracts revealed that PRMT1, PRMT4 and PRMT6 methylate some common substrate proteins, alongside pro-

tein substrates that are unique to each of these PRMTs [44]. Both PRMT4 and PRMT6 are involved in the generation of asymmetric dimethylation at Arg17 of histone 3 (H3R17me2a) and asymmetric dimethylation at Arg42 of histone 3 (H3R42me2a) in vivo [47,48]. Examples of common substrates include (i) the type1A topoisomerase enzyme, TOP3B, which is methylated by PRMT1, PRMT3 and PRMT6 enzymes [62] and (ii) the cell cycle inhibitor, p16 is methylated PRMT1, PRMT4 and PRMT6 enzymes [15]. All these observations suggest that PRMT6 can also methylate the substrates of other PRMTs in addition to its unique substrates. Nevertheless, the biochemical and structural mechanisms underlying how overlapping substrates are methylated by different PRMTs remains elusive.

3. Structural Attributes

PRMT6 of *Trypanosoma brucei*, mouse and human in complex with sinefungin (SNF) or SAH and/or short substrate peptide have been structurally characterized [63–65]. Mouse PRMT6 shares 91.5% sequence homology with human PRMT6 and 29% sequence homology with *T. brucei* PRMT6 [64]. All members of the PRMT family share a conserved catalytic PRMT core region with variable N-terminal regions. The overall structure of human PRMT6 is similar to that of other PRMT family members. PRMT6 consists of three structural components viz. (i) the N-terminal Rossmann fold, which contains the SAM binding pocket, (ii) the C-terminal β -barrel domain and (iii) a dimerization helix, which are located between the β 6 strand and β 7 strand of the C-terminal β -barrel domain (Figure 2A). A conserved proline (Pro186) in cis-conformation connects the N-terminal Rossmann fold and the C-terminal β -barrel domain [64,65]. The invariant residues in the SAM binding pocket of Rossmann fold interacts with the homocysteine carboxylate, adenine ring and ribose of SAH through hydrogen bonds and salt bridges [65] (Figure 2B).

Structural comparison of PRMT6 with other type I PRMT structures revealed two interesting features of PRMT6: (i) The conserved aromatic motif Y(F/Y)xxY at the N-terminal region covers the adenosine moiety of SAH as a lid in case of PRMT3 and PRMT4 structures [66–68], while in PRMT6 and PRMT1 this motif is positioned outwards from the SAH binding pocket [65,69,70] (Figure 2B). Since this aromatic motif is important for the SAH binding and catalysis of PRMT1 [70], it might adopt different conformations dynamically to facilitate the release of SAH during catalysis of PRMT1 and PRMT6. (ii) Similar to other type I PRMT members, PRMT6 also forms a dimer through the interaction of dimerization arm helices of one monomer with the N-terminal helices and the helices of Rossmann fold of the other monomer [65]. The dimerization arm of PRMT6 exhibits a different conformation and forms a flat ring dimer structure with a central cavity in contrast to the concave surface cavity formed by the other type I PRMT dimers [65,70,71]. This unique arrangement of the central cavity of PRMT6 dimer might influence the substrate selectivity of PRMT6.

Superimposition of the *T. brucei* PRMT7 (TbPRMT7) structure (PDBID: 4M38) [72] and modelling of the arginine residue into the active site of the human PRMT6 structure (PDBID: 5HZM) [65] revealed that the conserved glutamate Glu155 in the active site forms a hydrogen bond with the substrate arginine residue (Figure 2C). However, the other conserved glutamate, Glu164, which is part of the double E loop is directed outward from arginine in the active site. An outward direction of Glu164 was also observed upon the superimposition of the PRMT1-arginine-SAH complex structure [69] on the PRMT6 structure [65]. The corresponding glutamate Glu181 of TbPRMT7 and Glu444 of PRMT5 forms a hydrogen bond with the target arginine in TbPRMT7-H4R3 peptide-SAH and PRMT5-H4R3 peptide-SAH complexes respectively (Figure 2C) [72,73]. Moreover, the Glu164 residue points towards the active site in PRMT6 in complex with SAH and the inhibitor, EPZ0204111 [65]. Collectively, these observations suggest that the conserved Glu164 residue of the double E loop points towards the target arginine and forms a hydrogen bond or it points away from the active site, and this flexible nature of this residue might be important for the catalysis.

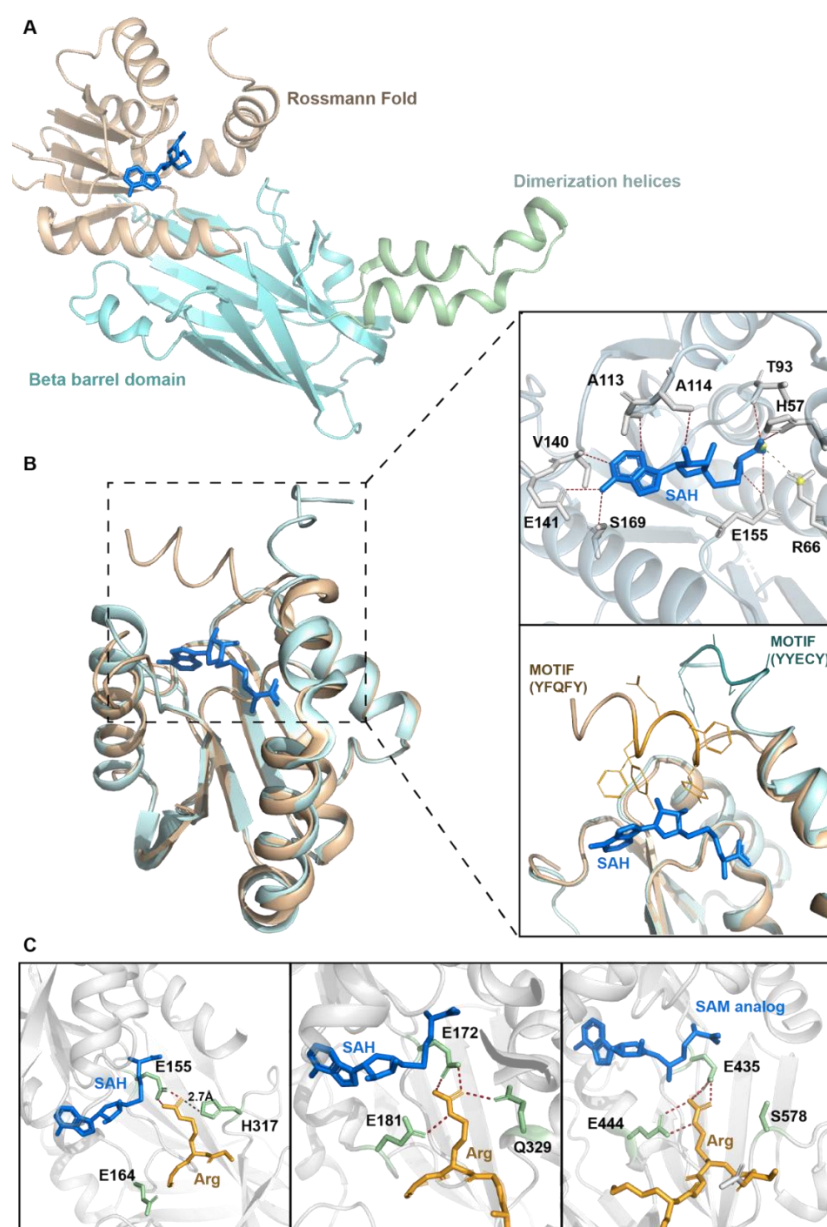


Figure 2. Structural attributes of PRMT6. (A) Crystal structure of the human PRMT6 (PDBID: 6W6D) in complex with SAH (marine blue). (B) Structural superimposition of the Rossmann fold region of PRMT6 (PDBID: 6W6D, cyan), PRMT4 (PDBID: 6IZQ, brown). Top inset shows the detailed interactions between PRMT6 and SAH (Top; PDBID: 6W6D). Polar contacts (red) and salt bridges (yellow) are displayed as dashed lines. PRMT6 is represented in cartoon and side chains of the residues (white) interacting with S-adenosyl-L-homocysteine (SAH; marine blue) are represented as sticks. Bottom inset shows the structural superimposition of the conserved motif from PRMT6 (Motif: YYECY) and PRMT4 (Motif: YFQFY). The sidechains of the motif residues are highlighted as wire-representations. (C) Structural comparison of the human PRMT6 (Left panel; PDBID: 5HZM) with *T. brucei* PRMT7 (Middle panel; PDBID: 4M38) and human PRMT5 (Right panel; PDBID: 4GQB) highlighting the active site in complex with the arginine (orange). SAH in the first two panels and S-adenosyl-L-methionine (SAM) analog in the third panel have been highlighted in marine blue. For the PRMT6 (left panel), arginine is modeled into the active site of human PRMT6 (PDBID: 5HZM) by superimposing the *T. brucei* PRMT7 structure (PDBID: 4M38). Distance between His317 and arginine N η 2 atom (left panel) is shown as black colored dashed line. Polar contacts are displayed as red colored dashed lines. Interacting residues side chains are represented as sticks (green).

The THW motif, present in the loop that connects the $\beta 11$ and $\beta 12$ of the β -barrel domain, is located in the active site of PRMT6 and is conserved among the type I PRMTs. His317 of the THW motif is likely to form a hydrogen bond with the $N\eta 2$ atom of the target arginine as it is within the distance of 2.7 Å (Figure 2C). This might impede the swapping of $N\eta 2$ and methyl $N\eta 1$ positions and thus preclude symmetric dimethylation. The corresponding residue in TbPRMT7 complex, Gln329, also forms a hydrogen bond with the $N\eta 2$ atom of the target arginine in a similar manner and hence prevents the symmetric dimethylation (Figure 2C) [65,72]. However, in case of the type II PRMT5 enzyme complex, the corresponding residue of His317 is Ser578, which does not form a hydrogen bond with $N\eta 2$ atom of the target arginine as it points away from the target arginine (Figure 2C). Such an arrangement allows the swapping of $N\eta 2$ and methyl $N\eta 1$ positions and facilitates the generation of symmetric dimethyl arginine [65,73]. Taken together, these findings and comparisons provide the plausible structural basis for the mechanism underlying PRMT6 generation of asymmetric dimethyl arginine.

4. Biological Roles of PRMT6

4.1. Epigenetic Functions of PRMT6

Post-translational modifications of the histone tails regulate the chromatin structure and control various chromatin-dependent processes including gene expression. PRMT6 is the major enzyme that generates asymmetric dimethylation at Arg2 of histone 3 (H3R2me2a) *in vivo* and regulates the global levels of H3R2me2a [4–6]. PRMT6-mediated H3R2me2a modifications are enriched in the gene body and promoter regions of inactive genes and inversely correlate with active H3K4me3 (trimethylation of histone 3 at Lys4) modifications in the promoter regions. The H3R2me2a modification is a repressive mark as its presence in the promoters negatively correlates with the transcript levels of the associated genes [4]. Not surprisingly, presence of the active histone mark H3K4me3 inhibits the PRMT6 activity on the H3 peptides [4,5]. The SET1/MLL family of enzymes catalyze the formation of the active H3K4me3 modification and these enzymes function as a complex with other protein factors [74–77]. The MLL complex does not show activity on the H3 peptides with H3R2me2a modification [4,6]. These findings explain the observed counter-correlation between the H3K4me3 and H3R2me2a modifications and the corresponding roles of methyltransferases at the promoter regions.

The majority of the reader proteins which recognize the H3K4me3 modification exhibit a reduced or non-detectable binding with the H3 peptides carrying the dual H3K4me3 and H3R2me2a modifications. This indicates that the presence of H3R2me2a modification inhibits the recognition of H3K4me3 modification by the reader proteins [5]. MLL complex activates the expression of HoxA genes and Myc targets genes by generating H3K4me3 modifications at their promoters [76,78–80] and the PRMT6 down regulates the expression of these genes [6]. The over-expression of PRMT6 represses the expression of HoxA2 by increasing the level of H3R2me2 marks and reducing H3K4me3 modifications near the transcription start site of the HoxA2 gene [6] (Figure 2A).

PRMT6 mediated H3R2me2a modifications tend to co-occur with H3K27me3 in a subset of silent gene promoters [12,80,81]. PRMT6 interacts with the polycomb repressive complexes (PRC) and silences the transcription of rostral HOXA genes by generating H3R2me2a and H3K27me3 modifications in their promoters [82]. Thrombospondin-1 (TSP-1) is a secretory protein which inhibits angiogenesis strongly and negatively affects cell migration [83–85]. In the U2OS osteosarcoma cells, PRMT6 has been shown to down regulate the expression of TSP-1 by introducing H3R2me2a modifications and reducing the active H3K4me3 modification in the TSP-1 promoter regions (Figure 3A). This negative regulation of TSP-1 by PRMT6 increases the migration and invasive properties of the U2OS cells [85]. However, this effect appears to be cell/cancer-type specific, as the over-expression of PRMT6 in human estrogen-sensitive breast cancer cells (MCF7) and the human prostate cancer cells (PC3) increases the TSP-1 expression and hence inhibits the movement and invasion of cancer cells [86]. Additional studies are

required to resolve this conundrum as to why enhanced levels of PRMT6 have opposing effects in different cancers.

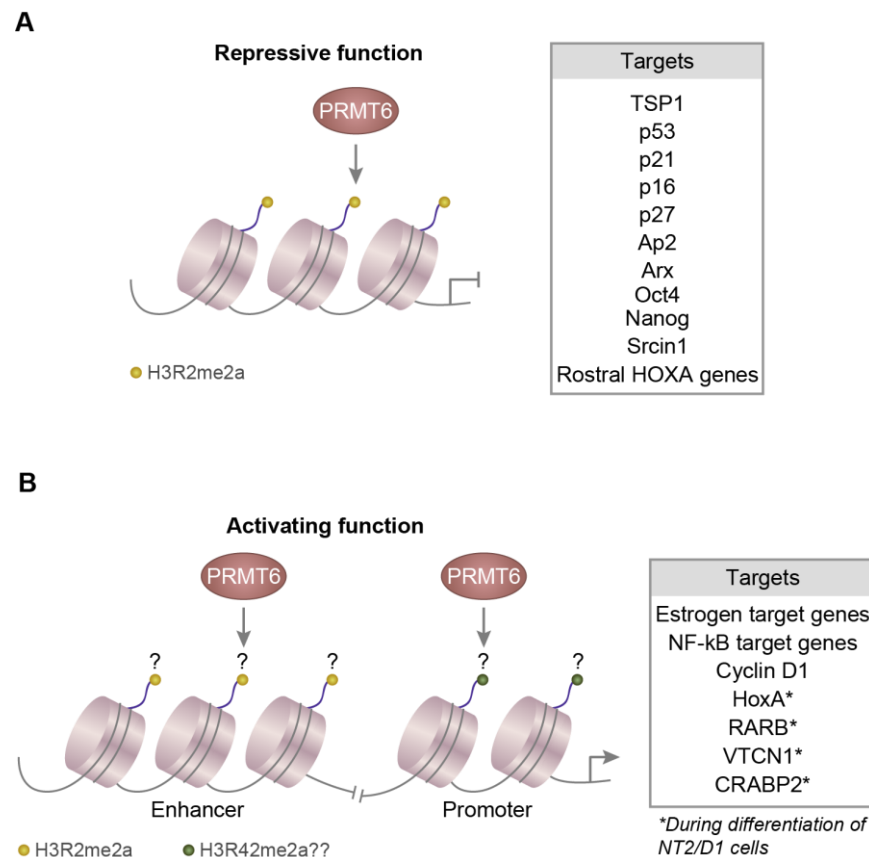


Figure 3. PRMT6 mediated epigenetic regulation of gene expression. (A) Schema highlighting the repressive role of PRMT6. PRMT6 generates H3R2me2a modifications at the promoters of the target genes and suppresses their expression. (B) Schematic representation of the transcriptional activation function of PRMT6. PRMT6 generates H3R2me2a modifications at the enhancers and probably H3R42me2a modifications at the promoters of the target genes and activates their expression. '?' indicates that the highlighted histone modifications are putative and need further characterization.

From a molecular point of view, PRMT6 promotes cell proliferation and contributes to the tumorigenic properties and prevents premature cellular senescence by downregulating the expression of tumor suppressor genes, p53, p21, p16 and p27. PRMT6 downregulates these tumor suppressors by generating the repressive H3R2me2a modifications in their promoters and other regulatory regions [16,17,20,87]. PRMT6 regulates adipocyte differentiation by interacting with PPAR γ and inhibiting its functions. PRMT6 suppresses the expression of the PPAR γ target gene, adipocyte protein 2 (Ap2) by binding to the PPAR responsive regulatory element in the promoter of the Ap2 along with PPAR γ and by adding repressive H3R2me2a modifications [88]. Aristaless Related Homeobox (Arx) is a lineage determining gene which is expressed exclusively in the pancreatic α cells. DNA methylation and PRMT6-mediated H3R2me2a modifications in the upstream regulatory regions of Arx gene suppresses its expression in pancreatic β cells [89]. Repeated cocaine exposure decreases the PRMT6 in dopamine D2 expressing medium spiny neurons (D2-MSNs) present in the nucleus accumbens of the basal forebrain. This leads to the decrease of H3R2me2a modifications and an increase in H3K4me3 modifications in the promoter region of Src kinase signaling inhibitor 1 (Srcin1) which in turn upregulates the Srcin 1 expression. The elevated levels of Srcin 1 inhibits the Src signaling, thereby reducing cocaine reward and the intent for the self-administration of cocaine [90] (Figure 3A).

PRMT6 and the associated H3R2me2a modifications increase globally during the differentiation of the mouse embryonic stem cells. Specifically, PRMT6 regulates the expression of the pluripotency genes, Oct4 and Nanog by modulating the levels of H3R2me2a and H3K4me3 modifications at their promoter regions [10]. During the megakaryocytic/erythroid lineage bifurcation of common hematopoietic progenitor cells, PRMT6 facilitates megakaryocytic differentiation by inhibiting the expression of erythroid genes. In the CD34 positive hematopoietic progenitor cells, the transcription factor RUNX1 interacts with PRMT6 and establishes the H3R2me2a modifications at the promoters of megakaryocytic genes [12,13]. During the megakaryocytic differentiation of the progenitor cells, PRMT6 dissociates from the RUNX1 co-repressor complex and facilitates the expression of megakaryocytic genes [12,13]. In addition, PRMT6 inhibits the expression of erythroid genes by generating the repressive H3R2me2a modifications in their promoter regions during megakaryocytic differentiation of the progenitor cells [91] (Figure 3A).

UHRF1 is the multi-domain protein factor which facilitates the recruitment of DNMT1 to the hemi-methylated CpG sites and the maintenance of DNA methylation pattern [92,93]. PRMT6 mediated H3R2me2a modifications inhibit the binding of UHRF1 to the chromatin which in turn negatively affects the DNA methylation by DNMT1 [21,94–97]. The high levels of PRMT6 in cancer cells lead to the global DNA hypomethylation and contribute to the carcinogenesis, possibly through the passive DNA demethylation [21]. The H3R2me2a modifications generated by PRMT6 play an important role in chromosome condensation during mitosis, because H3R2me2a recruits chromosomal passenger complex (CPC) to the chromosome upon mitotic entry and augments the H3S10 phosphorylation by Aurora B kinase which in turn facilitates the chromosome condensation [22].

In addition to the repressive epigenetic roles, PRMT6 also functions as a co-activator for steroid hormone receptors and this co-activator function requires the methyltransferase activity of PRMT6. PRMT6 promotes the expression of estrogen target genes and cell proliferation in an estrogen-dependent manner in MCF7 cells [7]. PRMT6 interacts with the transcription factor NF- κ B and serves as co-activator to facilitate the expression of NF- κ B target genes [24]. The transcription factor LEF1 activates the expression of cyclin D1 by recruiting PRMT6 to the promoter of cyclin D1 [98]. This co-activator function of PRMT6 might be due to the ability of PRMT6 to generate the active H3R42me2a modifications as well in the chromatin (Figure 3B).

A recent thorough genome wide study of PRMT6 mediated H3R2me2a modification in human embryonal carcinoma NT2/D1 cells strikingly revealed that this modification is associated with promoters, transcriptional start site and enhancer elements of active genes rather than repressed genes [99]. The promoter and TSS site associated H3R2me2a modifications suppress the transcription of the associated active genes by preventing the generation of active H3K4me3 modifications at these locations. However, the enhancer associated H3R2me2a modifications activate the transcription of the associated genes by facilitating the deposition of H3K4me1 and H3K27ac modifications [99]. Interestingly, the PRMT6 generated H3R2me2a modifications tend not to co-occur at the promoter and enhancer regions of the same genes [99]. Thus, the transcriptional outcome of H3R2me2a modifications is dependent on the genomic location of these modifications (Figure 3B).

In addition to H3R2 methylation, PRMT6 also methylates H4 at Arg3 residue (H4R3me2a) *in vitro* [6], H3 at Arg42 residue (H3R42me2a) [47] and H2A at Arg29 residue (H2AR29me2a) both *in vitro* and *in vivo* [49]. The PRMT6 mediated H2AR29me2a modifications are enriched in the promoter regions of the specific genes which are down regulated [49]. PRMT6 also methylates H3 at Arg17 residue (H3R17me2a) *in vitro* alongside the PRMT4 enzyme. H3R17me2a levels are increased during the mitosis [100] and this increase of H3R17me2a requires both PRMT4 and PRMT6 enzymes. Moreover, over-expression of PRMT6 increases the H3R17me2a modifications globally. All these findings suggest that PRMT6 is also involved in the deposition of H3R17me2a alongside PRMT4 [48]. Thus, PRMT6 mediated histone modifications affect diverse biological processes by regulating the gene expression, deposition of other histone modifications and DNA methylation.

4.2. Functional Outcomes of PRMT6 Mediated Methylation of Its Substrates

Below, we will discuss the different non-histone substrates of PRMT6, identified through targeted molecular and/or biochemical studies and their functional consequences, as applicable. Firstly, we will discuss the human substrates and then shed light on the current understanding of the viral proteins that are methylated by PRMT6 (Table 1).

Table 1. Non-histone substrate proteins of PRMT6 and the functional outcomes of their methylation by PRMT6.

S. No.	Substrate Proteins	Functional Outcome(s) of PRMT6 Mediated Methylation	Reference (PMIDs)
1.	HMGA1a	Might regulate the binding of HMGA1a with DNA [101–103].	16157300, 16293633, 17550233
2.	DNA Polymerase β	Increases the polymerase activity and facilitates the base excision repair [14].	16600869
3.	P16	Promotes the cell cycle by inhibiting P16 interaction with CDK4 [15,18].	23032699, 26622834
4.	P21	Promotes the phosphorylation of P21 and accumulation of P21 in cytoplasm [19].	26436589
5.	CRTC2	Promotes the CRTC2-CREG interaction and enhances the expression of gluconeogenic enzymes in hepatocytes [104].	24570487
6.	ER α	Might promote estrogen dependent functions of ER α [7,30].	24742914, 20047962
7.	AR	Inhibits the phosphorylation of AR and promotes the hormone dependent transactivation of AR [29].	25569348
8.	GPS2	Enhances the protein stability of GPS2 [105].	26070566
9.	TOP3B	Enhances the topoisomerase activity and facilitates TOP3B localization in stress granules [62].	29471495
10.	SIRT7	Inhibits SIRT7 deacetylase activity, thereby promoting mitochondrial biogenesis [106].	30420520
11.	FOXO3	Enhances FOXO3 activity and contributes to the muscle atrophy [107].	30653406
12.	PTEN	Inhibits Akt signaling and modulates global alternative splicing [31].	30886105
13.	HTT	Facilitates the axonal transport of organelles by HTT and enhances the neuronal viability [108].	33852844
14.	CRAF	Inhibits CRAF-RAS interaction and suppresses the MEK/ERK signaling in Hepatocellular Carcinoma (HCC) [32].	30332648
15.	BAG5	Promotes the degradation of the BAG5 interaction partner, HSC70 which in turn inhibits autophagy in HCC [109].	33186656
16.	RCC1	Facilitates association of RCC1 with chromatin and promotes mitosis in Glioblastoma [23].	33539787
17.	HIV1-TAT	(i) Increases TAT1 stability, (ii) excludes the Tat from the nucleolus and (iii) decreases its transactivation function [34,35,37,38].	19726520, 15596808, 26611710, 17267505
18.	HIV1-REV	Inhibits nuclear export function of REV [39].	17176473
19.	HIV1-Nucleocapsid protein (NC)	Decreases the capacity of NC to anneal the tRNA Lys to the primer site of viral RNA [40].	17415034
20.	pUL69 of human cytomegalovirus	The functional consequence of this methylation is unknown [41].	26178996

4.2.1. Substrates in Human Cells

(i). DNA repair protein-DNA Polymerase β

DNA Polymerase β plays an important role in the base excision repair [110–112]. PRMT6 interacts with and methylates DNA Polymerase β at Arg83 and Arg152 residues. Methylation of DNA Polymerase β by PRMT6 enhances its polymerase activity by increasing its processivity. The residues which are methylated by PRMT6 are important for efficient repair of DNA damage introduced by the alkylating agents [14].

(ii). Chromatin modifiers-HMGA1a, SIRT7

HMGA1 proteins are nuclear non-histone proteins which regulate the chromatin structure and gene expression [113–115]. PRMT6 has been shown to methylate HMGA1a

protein at Arg57 and Arg59 residues, both in vitro and in vivo [101–103]. These PRMT6 target residues are located in the second AT hook region of HMGA1a which is important for the binding of HMGA1a with DNA, suggesting that PRMT6 mediated methylation of HMGA1a might affect its binding with the DNA [102,103].

SIRT7, a deacetylase, catalyzes the removal of the acetylation modification of histone 3 at Lys18 (H3K18ac) and regulates many cellular processes including mitochondrial biogenesis [116–121]. PRMT6 interacts with SIRT7 and methylates it at Arg388. This methylation inhibits the deacetylase activity of SIRT7 and positively regulates mitochondrial biogenesis. The glucose availability regulates the PRMT6-mediated methylation of SIRT7 in an AMPK dependent manner [106]. Thus, the methylation of SIRT7 by PRMT6 serves as a link that connects mitochondrial biogenesis with glucose levels [106].

(iii). *Transcription regulators-CRTC2, FOXO3, GPS2 and TOP3B*

The transcription factor CREB (cAMP response element binding protein) and the CREB-regulated transcriptional coactivator 2 (CRTC2) activate the expression of gluconeogenic enzymes in the liver during fasting [122–125]. PRMT6 interacts with CRTC2 and generates asymmetric dimethylation modifications at several arginine residues of CRTC2. These PRMT6-mediated methylations of CRTC2 aid its association with CREB at the promoter regions and enhance the expression of gluconeogenic enzymes in hepatocytes [104,126].

FOXO3 is a multifunctional transcription factor and is implicated in various biological processes including gluconeogenesis, DNA repair, cell cycle autophagy, redox balance and proteostasis [127,128]. It is also involved in muscle atrophy by inducing protein degradation through the expression of muscle specific ubiquitin ligases [129–131]. The muscle specific knock out of PRMT1 increases the expression of autophagic markers and muscle specific ubiquitin ligases and promotes the muscle atrophy. Depletion of PRMT1 upregulates the expression of PRMT6 in muscle cells which in turn methylates FOXO3 at Arg118, Arg218 and Arg249. The PRMT6 mediated methylation of FOXO3 enhances its activity and contributes to the muscle atrophy [107].

G protein pathway suppressor 2 (GPS2) is a transcriptional regulator and is implicated in several cellular processes including cell cycle, apoptosis, bile acid synthesis and inflammation [132–138]. Methylation of GPS2 at Arg312 and Arg323 residues by PRMT6 promotes the association of GPS2 with TBL1, which inhibits the proteasomal degradation of GPS2, thereby leading to its enhanced stability, with implications across diverse cellular functions [105].

TOP3B is a type1A topoisomerase enzyme which resolves the topological strains of both DNA and RNA [139,140]. The histone arginine methylation reader protein, TDRD3 interacts with TOP3B and recruits it to the target chromatin regions wherein TOP3B executes its functions [141,142]. PRMT1, PRMT3 and PRMT6 methylates the Arg833 and Arg835 in the C-terminal region of TOP3B. The methylation of TOP3B by PRMT6 is required for (i) the efficient relaxation of supercoiled DNA and preventing the R-loop formation during transcription and (ii) localization of TOP3B to the stress granules [62]. The Tudor domain of TDRD3 recognizes the methylarginines of TOP3B which enhances TOP3B-TDRD3 interaction and facilitates the localization of TOP3B to stress granules [62].

(iv). *Cell cycle inhibitors and tumor suppressor-P16, P21 and PTEN*

In addition to suppressing the expression of the cell cycle inhibitors p16 and p21 through epigenetic modifications [16,17], PRMT6 also methylates p16 and p21 and negatively regulates their functions. PRMT6 methylates p16 at Arg22, Arg131 and Arg138 residues and promotes the cell cycle by inhibiting the interaction of p16 with CDK4 [15,18]. PRMT6 has been shown to methylate p21 at Arg156 residue both in vitro and in vivo. This methylation promotes the phosphorylation of p21 resulting in the accumulation of the protein in cytoplasm [19].

The phosphatase PTEN is a tumor suppressor gene which is often mutated in cancers [143,144]. PTEN negatively regulates AKT signaling by dephosphorylating the phosphatidylinositol-3,4,5-trisphosphate (PIP3) [145,146]. PRMT6 methylates PTEN at Arg135, which is frequently mutated in cancer. The methylation of PTEN by PRMT6 is

required for the efficient suppression of AKT signaling by PTEN and modulates the global alternative splicing of pre-mRNAs [31].

(v). *Hormonal receptors-ER α and AR*

PRMT6 interacts and methylates the nuclear receptor ER α . PRMT6 promotes the estrogen-dependent and estrogen-independent activities of ER α in a methyltransferase activity dependent and independent manner, respectively. The interaction of PRMT6 with ER α inhibits the ER α -HSP90 interaction and promotes ligand independent functions of ER α [30]. Though the methyltransferase activity of PRMT6 is required for the enhancement of estrogen dependent activities of ER α [7,30], the precise functional outcome(s) of the PRMT6 mediated methylation of ER α is unknown.

The expansion of a polyglutamine tract in the androgen receptor (AR) causes the spinobulbar muscular atrophy (SBMA) disease [147–150]. PRMT6 promotes the hormone dependent transactivation function of normal AR as well as the polyglutamine expanded AR (mutant AR) in a methyltransferase activity dependent manner. The enhancement of transactivation function by PRMT6 is more pronounced for mutant AR compared to the normal AR [29]. PRMT6 forms a complex with AR and methylates AR at the arginine residues in the Akt consensus motif and inhibits the phosphorylation of AR by the Akt. PRMT6 contributes to the toxicity of polyglutamine expanded AR through its enhanced transactivation and interaction with the mutant AR [29].

(vi). *Scaffold protein-HTT*

The polyglutamine expansion in the huntingtin (HTT) protein causes the neurodegenerative disorder Huntington's disease (HD). The scaffold protein, HTT facilitates the transport of organelles in the axons and dendrites of the neurons [108,151]. The polyglutamine expansion in the mutant HTT affects its axonal transport [152–155]. PRMT6 interacts with HTT protein and deposits asymmetric dimethylation at Arg118. PRMT6 mediated methylation of HTT is required for the efficient axonal transport of vesicles and the viability of neurons [108]. Overexpression of PRMT6 in HD cells rescued the axonal trafficking and the neuronal viability [108].

Besides the aforementioned substrates, PRMT6 also methylates snRNPB, MIF, TUBB2A and HSJ-2 in vitro. However, the functional consequences of these methylations are unknown and remain to be investigated [33].

4.2.2. Viral Substrates

Several proteins of human immunodeficiency virus type I (HIV-1) are methylated by PRMT6, as part of the host response to suppress viral infection/propagation. For instance, PRMT6 interacts with the Tat protein of HIV-1, a transcriptional activator that stimulates the transcription of the viral genes and facilitates the viral replication [156], and methylates it at Arg52 and Arg53 positions [34–36]. This PRMT6 mediated methylation of Tat (i) increases its stability, (ii) excludes the Tat from the nucleolus and (iii) decreases its transactivation function resulting in the reduced production of viral particles [34,35,37,38]. Mechanistically, PRMT6 mediated methylation of Tat inhibits its interaction with Tat transactivation region (TAR) of HIV-1 RNA and inhibits formation of Tat-TAR-cyclin T1 ternary complex, resulting in the compromised transactivation function of Tat [35]. However, ectopic expression of PRMT6 in A549 cells and HeLa cells did not show inhibition of transactivation function of Tat [36] (Table 1).

Besides Tat protein, PRMT6 also methylates other HIV-1 viral proteins [39,40], including the Rev protein at its N-terminal arginine rich motif [39]. The Rev protein of HIV1 facilitates the nuclear export of intron containing viral RNAs [157–159]. PRMT6-mediated methylation of Rev decreases its binding with the Rev response element (RRE) of the viral RNA and inhibits the nuclear export function of the Rev [39]. The nucleocapsid protein (NC) of HIV-1 is methylated at Arg10 and Arg32 positions by PRMT6. The NC protein plays an important role in the packing of the HIV1 RNAs and in the annealing of tRNA Lys to the primer binding site of viral

RNA [160–166]. PRMT6-mediated methylation of NC protein hampers its ability to anneal the tRNA Lys to the primer site of viral RNA [40] (Table 1).

The pUL69 protein of the human cytomegalovirus facilitates the export of the unspliced mRNAs from nucleus to the cytoplasm by interacting with host mRNA export factor UAP56 or URH49 [167,168]. PRMT6 interacts with pUL69 at its N-terminal region which is important for the pUL69-UAP56 or URH49 interactions [41]. It is possible that the pUL69-PRMT6 interaction might affect the mRNA export function of pUL69. PRMT6 also methylates the N-terminal region of pUL69 [41] but the functional consequence of this methylation is hitherto not known (Table 1).

Taken together, these findings demonstrate that PRMT6 restricts HIV1 replication and propagation of viral particles by methylating the viral proteins and inhibiting their functions. Hence, any intervention strategy which maintains the optimal level of PRMT6 in cells such as preventing the proteasomal degradation of PRMT6 or promoting the expression of PRMT6 might serve well to restrict HIV1 infection and hence disease progression.

5. Role of PRMT6 in Cancers

PRMT6 levels are elevated in several types of cancers and the depletion of PRMT6 inhibits the proliferation of lung and bladder cancer cells [42]. In the following sections, we will discuss the role of PRMT6 in different cancer types (Figure 4).

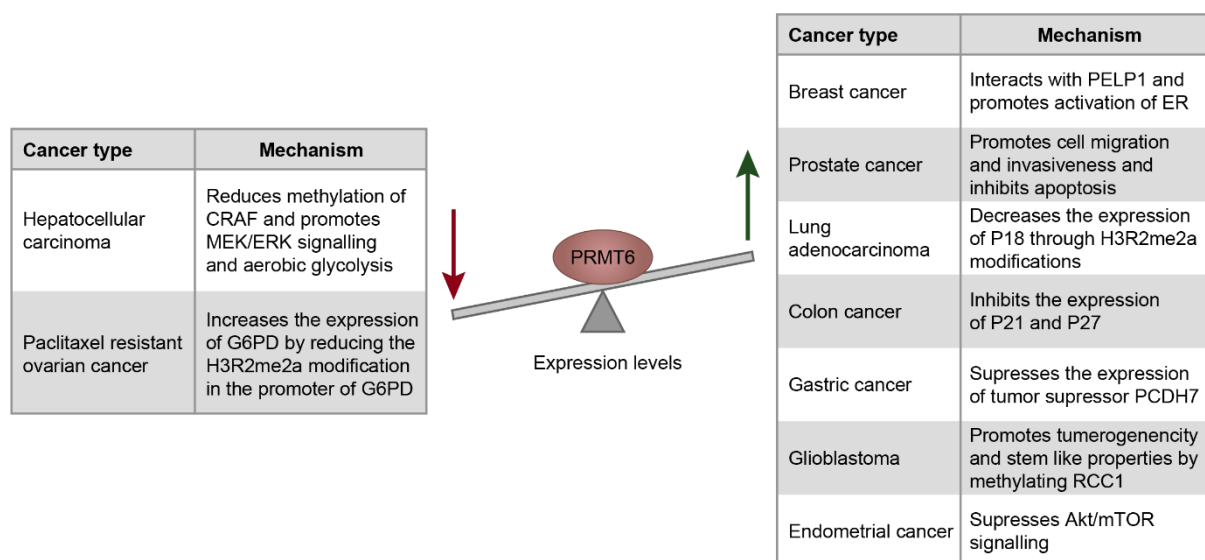


Figure 4. The role of PRMT6 in cancers. Schema representing the role of PRMT6 dysregulation in different cancers. The green arrow represents the upregulation of PRMT6 levels, while red arrow indicates the down regulation of PRMT6 levels in the corresponding cancer types, provided alongside in the table.

5.1. Breast, Prostate, Endometrial and Ovarian Cancers

PRMT6-mediated gene expression and alternative splicing changes are implicated in the pathophysiology of breast cancer [8]. The protooncogene PELP1 interacts with PRMT6 and promotes the activation of estrogen receptor, cell proliferation and clonogenic capacity of the breast cancer cells [169]. Overexpression of PRMT6 in the mammary glands of the mouse models promoted the tumorigenesis of mammary glands and deregulated Akt signaling in mammary epithelial cells [170].

PRMT6 levels are up-regulated in prostate cancer [171,172] and in endometrial cancer [173]. Depletion of PRMT6 in prostate cancer cells promotes apoptosis and decreases the cell migration and invasiveness properties [172]. Depletion of PRMT6 inhibits the endometrial cancer cell proliferation and migration by negatively regulating AKT/mTOR signaling [173].

Glucose-6-phosphate dehydrogenase (G6PD) levels are higher in paclitaxel resistant ovarian cancer cells compared to that of paclitaxel sensitive cancer cells. Depletion of G6PD in the paclitaxel resistant ovarian cancer cells increases its sensitivity to the paclitaxel treatment. PRMT6 is less abundant in paclitaxel resistant ovarian cancer cells compared to the sensitive cells. These low levels of PRMT6 lead to reduction of the repressive H3R2me2a modifications in the promoter region of G6PD resulting in the enhanced expression of G6PD which contributes to the paclitaxel resistance of the ovarian cancer cells [174].

5.2. Lung Cancer

PRMT6 levels are elevated in lung cancer [42,175]. Over-expression of PRMT6 in the lungs of mouse model enhanced the cell proliferation, promoting the lung tumor growth upon induction with a chemical carcinogen. PRMT6 interacts with interleukin enhancer binding protein 2 (ILF2) and activates the tumor associated macrophages [175]. PRMT6 levels are higher in the lung tissues of the patients with lung adenocarcinoma, which is associated with poor clinical outcomes [176]. Increased levels of PRMT6 reduces the expression of the cell cycle regulator p18 by increasing the amount of H3R2me2a and reducing the levels of H3K4me3 modifications. Depletion of PRMT6 activates the expression of p18 and inhibits the proliferation of lung adenocarcinoma cells [176].

5.3. Colon and Gastric Cancers

PRMT6 levels are elevated in colon cancer possibly due to the hypomethylation of PRMT6 promoter regions [177,178]. An abundance of PRMT6 is correlated with the shorter disease-free survival of colon cancer patients [178]. PPAR α regulates the expression of DNMT1 and PRMT6 in the intestinal cells and protects against colon cancer. Loss or depletion of PPAR α increases the levels of DNMT1 and PRMT6 which suppresses the expression of the cell cycle inhibitors p21 and p27 respectively and contributes to the colon carcinogenesis [179].

PRMT6 and H3R2me2a levels are elevated in gastric cancer (GC) and are correlated with poor prognosis. PRMT6 promotes the tumorigenicity and invasiveness of GC cells by silencing the expression of the tumor suppressor PCDH7 by depositing the repressive H3R2me2a marks at its promoter regions [180].

5.4. Glioblastoma

Regulator of chromosome condensin1 (RCC1) is a guanine nucleotide exchange factor for RAN-GTPase [181], which plays an important role in mitosis [182]. PRMT6 promotes the tumorigenicity and stem-like properties of the Glioblastoma stem cells (GSCs) by interacting with RCC1 and methylating it at Arg214. PRMT6-mediated methylation of RCC1 facilitates its association with chromatin and promotes mitosis through the generation of RAN-GTP [23,183].

5.5. Hepatocellular Carcinoma

RAF kinases activate the MEK/ERK signaling pathway and its dysregulation is implicated in cancers [184]. PRMT6 is downregulated in Hepatocellular carcinoma (HCC) and this downregulation is correlated with aggressive features of HCC. PRMT6 negatively regulates tumorigenic and stem-like properties of HCC. PRMT6 interacts and methylates CRAF at Arg100 which negatively regulates MEK/ERK signaling by inhibiting its interaction with RAS [32]. This negative regulation of MEK/ERK signaling also inhibits the aerobic glycolysis by preventing the ERK dependent nuclear localization of pyruvate kinase M2 (PKM2) [185]. In addition, the downregulation of PRMT6 promotes the autophagy and contributes to the tumorigenicity and cell survival in the tumor microenvironment. PRMT6 interacts with and methylates the co-chaperone Bcl-2, which is associated with athanogene 5 (BAG5) [186] at Arg15 and Arg24 and inhibits autophagy [109]. BAG5 forms a complex with the autophagic inducer, HSC70 [187,188] and the PRMT6-mediated methylation of BAG5 decreases the stability of HSC70 which in turn negatively regulates

autophagy [109]. Thus, the downregulation of PRMT6 contributes to the tumorigenic and stem-like properties of HCC.

Taken together, the elevated levels of PRMT6 are linked to carcinogenesis of many different types of cancers mediated through methylation of histone or non-histone substrates and/or protein interactions. Not surprisingly, downregulation of PRMT6 across these cancer types leads to a reduction in cell proliferation and invasiveness through different mechanisms (Figure 4). Depletion or knock-out of PRMT6 reduced (i) the cell proliferation and clonogenic capacity of the breast cancer cells [169], (ii) the cell migration and invasiveness of prostate cancer cells [172], (iii) endometrial cancer cell proliferation and migration [173], (iv) proliferation of lung adenocarcinoma cells [176] and (v) tumorigenic properties of gastric cancer cells [180]. It was reported that the inhibition of PRMT6 activity by the PRMT6 specific inhibitor EPZ020411 reduces the tumorigenicity of glioblastoma and improves its response to radiotherapy [23]. All these findings establish that PRMT6 is an important potential therapeutic target for various cancers. This necessitates studies that investigate the efficacy of PRMT6 specific inhibitors for cancer therapy. Contrary to these observations, downregulation of PRMT6 was observed in melanoma [189] and HCC [32].

6. Future Perspectives

PRMT6 downregulates the expression of the target genes by generating H3R2me2a modifications at their promoters. In addition to the repressive functions, PRMT6 also activates the expression of certain target genes. While the repressive functions of PRMT6 are well studied, we are beginning to understand the transcriptional activation functions of PRMT6. A combination of biochemical, structural and molecular studies are required to obtain a thorough understanding of the spatio-temporal context of the transcriptional activation functions of PRMT6. In addition to H3R2me2a modifications, PRMT6 also generates H2AR29me2a and H3R42me2a *in vivo*. We envision that future studies will delineate (i) the biological functions of these modifications, (ii) their regulatory roles on various cellular processes and (iii) their connections to the diseases. Since PRMT6 exhibits a relaxed substrate specificity in high throughput studies with peptides, it is very likely that PRMT6 has many more cellular protein substrates. This necessitates extensive efforts to identify the hitherto unidentified substrate proteins of PRMT6 and characterize the functional consequences of their PRMT6 mediated methylation. Structural studies of PRMT6 in complex with the substrate peptides and thorough kinetic studies are needed to delineate the actual kinetic mechanism of PRMT6 catalysis. The fact that PRMT6 methylates proteins of the RNA virus HIV-1 and modulates their functions necessitates a systematic investigation on the regulatory role(s) of PRMT6 on other RNA viral infections, especially SARS-CoV2. PRMT6 is elevated in several types of cancers and contributes to the tumorigenesis through various mechanisms. Hence, investigations based on the existing as well as novel potent and cell active PRMT6 inhibitors [190–194] for their therapeutic activities against various cancers especially in combination with the standard anti-cancer drugs could pave a way for targeted cancer interventions.

Author Contributions: S.G. and A.D. pursued literature search and prepared the first draft of the review. All authors were involved in the preparation of the illustrations. All authors edited the manuscript and agreed to the published version of the manuscript.

Funding: We gratefully acknowledge funding support from Board of Research in Nuclear Sciences (Grant No 37(1)/14/17/2017-BRNS/37019 to AD), Indian Council of Medical Research (Senior Research Fellowship to SG), Prime Minister's Research Fellowship (to AKS), Science & Engineering Research Board (National Post-Doctoral Fellowship to RVK, SRG/2019/001785 to SC), and Department of Biotechnology (Ramalingaswami Re-entry Fellowship, BT/RLF/Re-entry/05/2018 to SC), Government of India.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Guccione, E.; Richard, S. The regulation, functions and clinical relevance of arginine methylation. *Nat. Rev. Mol. Cell Biol.* **2019**, *20*, 642–657. [[CrossRef](#)] [[PubMed](#)]
2. Fulton, M.D.; Brown, T.; Zheng, Y.G. The Biological Axis of Protein Arginine Methylation and Asymmetric Dimethylarginine. *Int. J. Mol. Sci.* **2019**, *20*, 3322. [[CrossRef](#)] [[PubMed](#)]
3. Bedford, M.T.; Clarke, S.G. Protein Arginine Methylation in Mammals: Who, What, and Why. *Mol. Cell* **2009**, *33*, 1–13. [[CrossRef](#)] [[PubMed](#)]
4. Guccione, E.; Bassi, C.; Casadio, F.; Martinato, F.; Cesaroni, M.; Schuchloutz, H.; Lüscher, B.; Amati, B. Methylation of histone H3R2 by PRMT6 and H3K4 by an MLL complex are mutually exclusive. *Nature* **2007**, *449*, 933–937. [[CrossRef](#)] [[PubMed](#)]
5. Iberg, A.N.; Espejo, A.; Cheng, D.; Kim, D.; Michaud-Levesque, J.; Richard, S.; Bedford, M.T. Arginine methylation of the histone H3 tail impedes effector binding. *J. Biol. Chem.* **2008**, *283*, 3006–3010. [[CrossRef](#)] [[PubMed](#)]
6. Hyllus, D.; Stein, C.; Schnabel, K.; Schiltz, E.; Imhof, A.; Dou, Y.; Hsieh, J.; Bauer, U.M. PRMT6-mediated methylation of R2 in histone H3 antagonizes H3 K4 trimethylation. *Genes Dev.* **2007**, *21*, 3369–3380. [[CrossRef](#)]
7. Harrison, M.J.; Tang, Y.H.; Dowhan, D.H. Protein arginine methyltransferase 6 regulates multiple aspects of gene expression. *Nucleic Acids Res.* **2010**, *38*, 2201–2216. [[CrossRef](#)]
8. Dowhan, D.H.; Harrison, M.J.; Eriksson, N.A.; Bailey, P.; Pearen, M.A.; Fuller, P.J.; Funder, J.W.; Simpson, E.R.; Leedman, P.J.; Tilley, W.D.; et al. Protein arginine methyltransferase 6-dependent gene expression and splicing: Association with breast cancer outcomes. *Endocr. Relat. Cancer* **2012**, *19*, 509–526. [[CrossRef](#)]
9. Zhao, X.X.; Zhang, Y.B.; Ni, P.L.; Wu, Z.L.; Yan, Y.C.; Li, Y.P. Protein arginine methyltransferase 6 (Prmt6) is essential for early zebrafish development through the direct suppression of gadd45 α stress sensor gene. *J. Biol. Chem.* **2016**, *291*, 402–412. [[CrossRef](#)]
10. Lee, Y.H.; Ma, H.; Tan, T.Z.; Ng, S.S.; Soong, R.; Mori, S.; Fu, X.Y.; Zernicka-Goetz, M.; Wu, Q. Protein arginine methyltransferase 6 regulates embryonic stem cell identity. *Stem Cells Dev.* **2012**, *21*, 2613–2622. [[CrossRef](#)] [[PubMed](#)]
11. Li, Z.; Wang, P.; Li, J.; Xie, Z.; Cen, S.; Li, M.; Liu, W.; Ye, G.; Zheng, G.; Ma, M.; et al. The N 6-methyladenosine demethylase ALKBH5 negatively regulates the osteogenic differentiation of mesenchymal stem cells through PRMT6. *Cell Death Dis.* **2021**, *12*, 578. [[CrossRef](#)]
12. Herglotz, J.; Kuvardina, O.N.; Kolodziej, S.; Kumar, A.; Hussong, H.; Grez, M.; Lausen, J. Histone arginine methylation keeps RUNX1 target genes in an intermediate state. *Oncogene* **2013**, *32*, 2565–2575. [[CrossRef](#)]
13. Lausen, J. Contributions of the histone arginine methyltransferase PRMT6 to the epigenetic function of RUNX1. *Crit. Rev. Eukaryot. Gene Expr.* **2013**, *23*, 265–274. [[CrossRef](#)] [[PubMed](#)]
14. El-Andaloussi, N.; Valovka, T.; Toueille, M.; Steinacher, R.; Focke, F.; Gehrig, P.; Covic, M.; Hassa, P.O.; Schär, P.; Hübscher, U.; et al. Arginine Methylation Regulates DNA Polymerase β . *Mol. Cell* **2006**, *22*, 51–62. [[CrossRef](#)] [[PubMed](#)]
15. Ma, W.L.; Wang, L.; Liu, L.X.; Wang, X.L. Effect of phosphorylation and methylation on the function of the p16INK4a protein in non-small cell lung cancer A549 cells. *Oncol. Lett.* **2015**, *10*, 2277–2282. [[CrossRef](#)] [[PubMed](#)]
16. Stein, C.; Riedl, S.; Rüttnick, D.; Nötzold, R.R.; Bauer, U.M. The arginine methyltransferase PRMT6 regulates cell proliferation and senescence through transcriptional repression of tumor suppressor genes. *Nucleic Acids Res.* **2012**, *40*, 9522–9533. [[CrossRef](#)]
17. Kleinschmidt, M.A.; de Graaf, P.; van Teeffelen, H.A.A.M.; Timmers, H.T.M. Cell cycle regulation by the PRMT6 arginine methyltransferase through repression of cyclin-dependent kinase inhibitors. *PLoS ONE* **2012**, *7*, e0041446. [[CrossRef](#)]
18. Wang, X.; Huang, Y.; Zhao, J.; Zhang, Y.; Lu, J.; Huang, B. Suppression of PRMT6-mediated arginine methylation of p16 protein potentiates its ability to arrest A549 cell proliferation. *Int. J. Biochem. Cell Biol.* **2012**, *44*, 2333–2341. [[CrossRef](#)]
19. Nakakido, M.; Deng, Z.; Suzuki, T.; Dohmae, N.; Nakamura, Y.; Hamamoto, R. PRMT6 increases cytoplasmic localization of p21CDKN1A in cancer cells through arginine methylation and makes more resistant to cytotoxic agents. *Oncotarget* **2015**, *6*, 30957–30967. [[CrossRef](#)]
20. Neault, M.; Mallette, F.A.; Vogel, G.; Michaud-Levesque, J.; Richard, S. Ablation of PRMT6 reveals a role as a negative transcriptional regulator of the p53 tumor suppressor. *Nucleic Acids Res.* **2012**, *40*, 9513–9521. [[CrossRef](#)]
21. Veland, N.; Hardikar, S.; Zhong, Y.; Gayatri, S.; Dan, J.; Strahl, B.D.; Rothbart, S.B.; Bedford, M.T.; Chen, T. The Arginine Methyltransferase PRMT6 Regulates DNA Methylation and Contributes to Global DNA Hypomethylation in Cancer. *Cell Rep.* **2017**, *21*, 3390–3397. [[CrossRef](#)] [[PubMed](#)]
22. Kim, S.; Kim, N.H.; Park, J.E.; Hwang, J.W.; Myung, N.; Hwang, K.T.; Kim, Y.A.Y.K.; Jang, C.Y.; Kim, Y.A.Y.K. PRMT6-mediated H3R2me2a guides Aurora B to chromosome arms for proper chromosome segregation. *Nat. Commun.* **2020**, *11*, 612. [[CrossRef](#)] [[PubMed](#)]
23. Huang, T.; Yang, Y.; Song, X.; Wan, X.; Wu, B.; Sastry, N.; Horbinski, C.M.; Zeng, C.; Tiek, D.; Goenka, A.; et al. PRMT6 methylation of RCC1 regulates mitosis, tumorigenicity, and radiation response of glioblastoma stem cells. *Mol. Cell* **2021**, *81*, 1276–1291.e9. [[CrossRef](#)]
24. Di Lorenzo, A.; Yang, Y.; Macaluso, M.; Bedford, M.T. A gain-of-function mouse model identifies PRMT6 as a NF- κ B coactivator. *Nucleic Acids Res.* **2014**, *42*, 8297–8309. [[CrossRef](#)]

25. Tsai, K.D.; Lee, W.X.; Chen, W.; Chen, B.Y.; Chen, K.L.; Hsiao, T.C.; Wang, S.H.; Lee, Y.J.; Liang, S.Y.; Shieh, J.C.; et al. Upregulation of PRMT6 by LPS suppresses Klotho expression through interaction with NF- κ B in glomerular mesangial cells. *J. Cell. Biochem.* **2018**, *119*, 3404–3416. [[CrossRef](#)] [[PubMed](#)]
26. Stavride, P.; Arampatzi, P.; Papamatheakis, J. Differential regulation of MHCII genes by PRMT6, via an AT-hook motif of RFX5. *Mol. Immunol.* **2013**, *56*, 390–398. [[CrossRef](#)]
27. Zhang, H.; Han, C.; Li, T.; Li, N.; Cao, X. The methyltransferase PRMT6 attenuates antiviral innate immunity by blocking TBK1–IRF3 signaling. *Cell. Mol. Immunol.* **2019**, *16*, 800–809. [[CrossRef](#)] [[PubMed](#)]
28. Luo, M.; Li, Y.; Guo, H.; Lin, S.; Chen, J.; Ma, Q.; Gu, Y.; Jiang, Z.; Gui, Y. Protein arginine methyltransferase 6 involved in germ cell viability during spermatogenesis and down-regulated by the androgen receptor. *Int. J. Mol. Sci.* **2015**, *16*, 29467–29481. [[CrossRef](#)]
29. Scaramuzzino, C.; Casci, I.; Parodi, S.; Lievens, P.M.J.; Polanco, M.J.; Milioto, C.; Chivet, M.; Monaghan, J.; Mishra, A.; Badders, N.; et al. Protein Arginine Methyltransferase 6 Enhances Polyglutamine-Expanded Androgen Receptor Function and Toxicity in Spinal and Bulbar Muscular Atrophy. *Neuron* **2015**, *85*, 88–100. [[CrossRef](#)]
30. Sun, Y.; Chung, H.H.; Woo, A.R.E.; Lin, V.C.L. Protein arginine methyltransferase 6 enhances ligand-dependent and -independent activity of estrogen receptor α via distinct mechanisms. *Biochim. Biophys. Acta-Mol. Cell Res.* **2014**, *1843*, 2067–2078. [[CrossRef](#)]
31. Feng, J.; Dang, Y.; Zhang, W.; Zhao, X.; Zhang, C.; Hou, Z.; Jin, Y.; McNutt, M.A.; Marks, A.R.; Yin, Y. PTEN arginine methylation by PRMT6 suppresses PI3K–AKT signaling and modulates pre-mRNA splicing. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 6868–6877. [[CrossRef](#)] [[PubMed](#)]
32. Chan, L.H.; Zhou, L.; Ng, K.Y.; Wong, T.L.; Lee, T.K.; Sharma, R.; Loong, J.H.; Ching, Y.P.; Yuan, Y.F.; Xie, D.; et al. PRMT6 Regulates RAS/RAF Binding and MEK/ERK-Mediated Cancer Stemness Activities in Hepatocellular Carcinoma through CRAF Methylation. *Cell Rep.* **2018**, *25*, 690–701.e8. [[CrossRef](#)] [[PubMed](#)]
33. Lo Sardo, A.; Altamura, S.; Pegoraro, S.; Maurizio, E.; Sgarra, R.; Manfioletti, G. Identification and Characterization of New Molecular Partners for the Protein Arginine Methyltransferase 6 (PRMT6). *PLoS ONE* **2013**, *8*, e0053750. [[CrossRef](#)]
34. Boulanger, M.-C.; Liang, C.; Russell, R.S.; Lin, R.; Bedford, M.T.; Wainberg, M.A.; Richard, S. Methylation of Tat by PRMT6 Regulates Human Immunodeficiency Virus Type 1 Gene Expression. *J. Virol.* **2005**, *79*, 124–131. [[CrossRef](#)] [[PubMed](#)]
35. Xie, B.; Invernizzi, C.F.; Richard, S.; Wainberg, M.A. Arginine Methylation of the Human Immunodeficiency Virus Type 1 Tat Protein by PRMT6 Negatively Affects Tat Interactions with both Cyclin T1 and the Tat Transactivation Region. *J. Virol.* **2007**, *81*, 4226–4234. [[CrossRef](#)] [[PubMed](#)]
36. Sivakumaran, H.; Lin, M.H.; Apolloni, A.; Cutillas, V.; Jin, H.; Li, D.; Wei, T.; Harrich, D. Overexpression of PRMT6 does not suppress HIV-1 Tat transactivation in cells naturally lacking PRMT6. *Virol. J.* **2013**, *10*, 207. [[CrossRef](#)] [[PubMed](#)]
37. Sivakumaran, H.; van der Horst, A.; Fulcher, A.J.; Apolloni, A.; Lin, M.-H.; Jans, D.A.; Harrich, D. Arginine Methylation Increases the Stability of Human Immunodeficiency Virus Type 1 Tat. *J. Virol.* **2009**, *83*, 11694–11703. [[CrossRef](#)]
38. Fulcher, A.J.; Sivakumaran, H.; Jin, H.; Rawle, D.J.; Harrich, D.; Jans, D.A. The protein arginine methyltransferase PRMT6 inhibits HIV-1 Tat nucleolar retention. *Biochim. Biophys. Acta-Mol. Cell Res.* **2016**, *1863*, 254–262. [[CrossRef](#)]
39. Invernizzi, C.F.; Xie, B.; Richard, S.; Wainberg, M.A. PRMT6 diminishes HIV-1 Rev binding to and export of viral RNA. *Retrovirology* **2006**, *3*, 93. [[CrossRef](#)]
40. Invernizzi, C.F.; Xie, B.; Frankel, F.A.; Feldhammer, M.; Roy, B.B.; Richard, S.; Wainberg, M.A. Arginine methylation of the HIV-1 nucleocapsid protein results in its diminished function. *AIDS* **2007**, *21*, 795–805. [[CrossRef](#)]
41. Thomas, M.; Sonntag, E.; Müller, R.; Schmidt, S.; Zielke, B.; Fossen, T.; Stamminger, T. pUL69 of Human Cytomegalovirus Recruits the Cellular Protein Arginine Methyltransferase 6 via a Domain That Is Crucial for mRNA Export and Efficient Viral Replication. *J. Virol.* **2015**, *89*, 9601–9615. [[CrossRef](#)]
42. Yoshimatsu, M.; Toyokawa, G.; Hayami, S.; Unoki, M.; Tsunoda, T.; Field, H.I.; Kelly, J.D.; Neal, D.E.; Maehara, Y.; Ponder, B.A.J.; et al. Dysregulation of PRMT1 and PRMT6, Type I arginine methyltransferases, is involved in various types of human cancers. *Int. J. Cancer* **2011**, *128*, 562–573. [[CrossRef](#)]
43. Raveendran, V.V.; Al-Haffar, K.; Kunhi, M.; Belhaj, K.; Al-Habeeb, W.; Al-Buraiki, J.; Eyjolsson, A.; Poizat, C. Protein arginine methyltransferase 6 mediates cardiac hypertrophy by differential regulation of histone H3 arginine methylation. *Heliyon* **2020**, *6*, e03864. [[CrossRef](#)]
44. Frankel, A.; Yadav, N.; Lee, J.; Branscombe, T.L.; Clarke, S.; Bedford, M.T. The novel human protein arginine N-methyltransferase PRMT6 is a nuclear enzyme displaying unique substrate specificity. *J. Biol. Chem.* **2002**, *277*, 3537–3543. [[CrossRef](#)] [[PubMed](#)]
45. Chen, W.; Gao, D.; Xie, L.; Wang, A.; Zhao, H.; Guo, C.; Sun, Y.; Nie, Y.; Hong, A.; Xiong, S. SCF-FBXO24 regulates cell proliferation by mediating ubiquitination and degradation of PRMT6. *Biochem. Biophys. Res. Commun.* **2020**, *530*, 75–81. [[CrossRef](#)] [[PubMed](#)]
46. Li, T.; He, X.; Luo, L.; Zeng, H.; Ren, S.; Chen, Y. F-Box Protein FBXW17-Mediated Proteasomal Degradation of Protein Methyltransferase PRMT6 Exaggerates CSE-Induced Lung Epithelial Inflammation and Apoptosis. *Front. Cell Dev. Biol.* **2021**, *9*, 599020. [[CrossRef](#)]
47. Casadio, F.; Lu, X.; Pollock, S.B.; LeRoy, G.; Garcia, B.A.; Muir, T.W.; Roeder, R.G.; Allis, C.D. H3R42me2a is a histone modification with positive transcriptional effects. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 14894–14899. [[CrossRef](#)] [[PubMed](#)]
48. Cheng, D.; Gao, G.; Di Lorenzo, A.; Jayne, S.; Hottiger, M.O.; Richard, S.; Bedford, M.T. Genetic evidence for partial redundancy between the arginine methyltransferases CARM1 and PRMT6. *J. Biol. Chem.* **2020**, *295*, 17060–17070. [[CrossRef](#)] [[PubMed](#)]

49. Waldmann, T.; Izzo, A.; Kamieniarz, K.; Richter, F.; Vogler, C.; Sarg, B.; Lindner, H.; Young, N.L.; Mittler, G.; Garcia, B.A.; et al. Methylation of H2AR29 is a novel repressive PRMT6 target. *Epigenetics Chromatin* **2011**, *4*, 11. [[CrossRef](#)]
50. Lischwe, M.A.; Ahn, Y.S.; Yeoman, L.C.; Busch, H.; Cook, R.G. Clustering of Glycine and NG,NG-Dimethylarginine in Nucleolar Protein C23. *Biochemistry* **1985**, *24*, 6025–6028. [[CrossRef](#)]
51. Tang, J.; Gary, J.D.; Clarke, S.; Herschman, H.R. PRMT 3, a type I protein arginine N-methyltransferase that differs from PRMT1 in its oligomerization, subcellular localization, substrate specificity, and regulation. *J. Biol. Chem.* **1998**, *273*, 16935–16945. [[CrossRef](#)] [[PubMed](#)]
52. Zhang, X.; Zhou, L.; Cheng, X. Crystal structure of the conserved core of protein arginine methyltransferase PRMT3. *EMBO J.* **2000**, *19*, 3509–3519. [[CrossRef](#)] [[PubMed](#)]
53. Lakowski, T.M.; Frankel, A. A kinetic study of human protein arginine N-methyltransferase 6 reveals a distributive mechanism. *J. Biol. Chem.* **2008**, *283*, 10015–10025. [[CrossRef](#)] [[PubMed](#)]
54. Frankel, A. Inconvenient truths for PRMT6 kinetic studies. *J. Biol. Chem.* **2012**, *287*, 9512. [[CrossRef](#)]
55. Obianyo, O.; Thompson, P.R. Kinetic mechanism of protein arginine methyltransferase 6 (PRMT6). *J. Biol. Chem.* **2012**, *287*, 6062–6071. [[CrossRef](#)] [[PubMed](#)]
56. Obianyo, O.; Causey, C.P.; Osborne, T.C.; Jones, J.E.; Lee, Y.H.; Stallcup, M.R.; Thompson, P.R. A chloroacetamide-based inactivator of protein arginine methyltransferase 1: Design, synthesis, and in vitro and in vivo evaluation. *ChemBioChem* **2010**, *11*, 1219–1223. [[CrossRef](#)]
57. Singhroy, D.N.; Mesplède, T.; Sabbah, A.; Quashie, P.K.; Falgouty, J.P.; Wainberg, M.A. Automethylation of protein arginine methyltransferase 6 (PRMT6) regulates its stability and its anti-HIV-1 activity. *Retrovirology* **2013**, *10*, 27880. [[CrossRef](#)]
58. Hamey, J.J.; Rakow, S.; Boucharde, C.; Senst, J.M.; Kolb, P.; Bauer, U.M.; Wilkins, M.R.; Hart-Smith, G. Systematic investigation of PRMT6 substrate recognition reveals broad specificity with a preference for an RG motif or basic and bulky residues. *FEBS J.* **2021**. [[CrossRef](#)]
59. Wooderchak, W.L.; Zang, T.; Zhou, Z.S.; Acuña, M.; Tahara, S.M.; Hevel, J.M. Substrate profiling of PRMT1 reveals amino acid sequences that extend beyond the “RGG” paradigm. *Biochemistry* **2008**, *47*, 9456–9466. [[CrossRef](#)]
60. Hamey, J.J.; Separovich, R.J.; Wilkins, M.R. MT-MAMS: Protein Methyltransferase Motif Analysis by Mass Spectrometry. *J. Proteome Res.* **2018**, *17*, 3485–3491. [[CrossRef](#)]
61. Shishkova, E.; Zeng, H.; Liu, F.; Kwiecien, N.W.; Hebert, A.S.; Coon, J.J.; Xu, W. Global mapping of CARM1 substrates defines enzyme specificity and substrate recognition. *Nat. Commun.* **2017**, *8*, 15571. [[CrossRef](#)]
62. Huang, L.; Wang, Z.; Narayanan, N.; Yang, Y. Arginine methylation of the C-terminus RGG motif promotes TOP3B topoisomerase activity and stress granule localization. *Nucleic Acids Res.* **2018**, *46*, 3061–3074. [[CrossRef](#)]
63. Wang, C.; Zhu, Y.; Chen, J.; Li, X.; Peng, J.; Chen, J.; Zou, Y.; Zhang, Z.; Jin, H.; Yang, P.; et al. Crystal structure of arginine methyltransferase 6 from *Trypanosoma brucei*. *PLoS ONE* **2014**, *9*, e0087267. [[CrossRef](#)]
64. Bonnefond, L.; Stojko, J.; Mailliot, J.; Troffer-Charlier, N.; Cura, V.; Wurtz, J.M.; Cianférani, S.; Cavarelli, J. Functional insights from high resolution structures of mouse protein arginine methyltransferase 6. *J. Struct. Biol.* **2015**, *191*, 175–183. [[CrossRef](#)]
65. Wu, H.; Zheng, W.; Eram, M.S.; Vhuiyan, M.; Dong, A.; Zeng, H.; He, H.; Brown, P.; Frankel, A.; Vedadi, M.; et al. Structural basis of arginine asymmetrical dimethylation by PRMT6. *Biochem. J.* **2016**, *473*, 3049–3063. [[CrossRef](#)] [[PubMed](#)]
66. Goulet, I.; Gauvin, G.; Boisvenue, S.; Côté, J. Alternative splicing yields protein arginine methyltransferase 1 isoforms with distinct activity, substrate specificity, and subcellular localization. *J. Biol. Chem.* **2007**, *282*, 33009–33021. [[CrossRef](#)] [[PubMed](#)]
67. Siarheyeva, A.; Senisterra, G.; Allali-Hassani, A.; Dong, A.; Dobrovetsky, E.; Wasney, G.A.; Chau, I.; Marcellus, R.; Hajian, T.; Liu, F.; et al. An allosteric inhibitor of protein arginine methyltransferase 3. *Structure* **2012**, *20*, 1425–1435. [[CrossRef](#)]
68. Yue, W.W.; Hassler, M.; Roe, S.M.; Thompson-Vale, V.; Pearl, L.H. Insights into histone code syntax from structural and biochemical studies of CARM1 methyltransferase. *EMBO J.* **2007**, *26*, 4402–4412. [[CrossRef](#)] [[PubMed](#)]
69. Weiss, V.H.; McBride, A.E.; Soriano, M.A.; Filman, D.J.; Silver, P.A.; Hogle, J.M. The structure and oligomerization of the yeast arginine methyltransferase, Hmt1. *Nat. Struct. Biol.* **2000**, *7*, 1165–1171. [[CrossRef](#)] [[PubMed](#)]
70. Zhang, X.; Cheng, X. Structure of the predominant protein arginine methyltransferase PRMT1 and analysis of its binding to substrate peptides. *Structure* **2003**, *11*, 509–520. [[CrossRef](#)]
71. Troffer-Charlier, N.; Cura, V.; Hassenboehler, P.; Moras, D.; Cavarelli, J. Functional insights from structures of coactivator-associated arginine methyltransferase 1 domains. *EMBO J.* **2007**, *26*, 4391–4401. [[CrossRef](#)]
72. Wang, C.; Zhu, Y.; Caceres, T.B.; Liu, L.; Peng, J.; Wang, J.; Chen, J.; Chen, X.; Zhang, Z.; Zuo, X.; et al. Structural determinants for the strict monomethylation activity by *trypanosoma brucei* protein arginine methyltransferase 7. *Structure* **2014**, *22*, 756–768. [[CrossRef](#)] [[PubMed](#)]
73. Antonysamy, S.; Bonday, Z.; Campbell, R.M.; Doyle, B.; Druzina, Z.; Gheyi, T.; Han, B.; Jungheim, L.N.; Qian, Y.; Rauch, C.; et al. Crystal structure of the human PRMT5:MEP50 complex. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 17960–17965. [[CrossRef](#)] [[PubMed](#)]
74. Tenney, K.; Shilatifard, A. A COMPASS in the voyage of defining the role of trithorax/MLL-containing complexes: Linking leukemogenesis to covalent modifications of chromatin. *J. Cell. Biochem.* **2005**, *95*, 429–436. [[CrossRef](#)]
75. Wysocka, J.; Myers, M.P.; Laherty, C.D.; Eisenman, R.N.; Herr, W. Human Sin3 deacetylase and trithorax-related Set1/Ash2 histone H3-K4 methyltransferase are tethered together selectively by the cell-proliferation factor HCF-1. *Genes Dev.* **2003**, *17*, 896–911. [[CrossRef](#)]

76. Hughes, C.M.; Rozenblatt-Rosen, O.; Milne, T.A.; Copeland, T.D.; Levine, S.S.; Lee, J.C.; Hayes, D.N.; Shanmugam, K.S.; Bhattacharjee, A.; Biondi, C.A.; et al. Menin associates with a trithorax family histone methyltransferase complex and with the Hoxc8 locus. *Mol. Cell* **2004**, *13*, 587–597. [[CrossRef](#)]
77. Steward, M.M.; Lee, J.S.; O'Donovan, A.; Wyatt, M.; Bernstein, B.E.; Shilatifard, A. Molecular regulation of H3K4 trimethylation by ASH2L, a shared subunit of MLL complexes. *Nat. Struct. Mol. Biol.* **2006**, *13*, 852–854. [[CrossRef](#)]
78. Milne, T.A.; Briggs, S.D.; Brock, H.W.; Martin, M.E.; Gibbs, D.; Allis, C.D.; Hess, J.L. MLL targets SET domain methyltransferase activity to Hox gene promoters. *Mol. Cell* **2002**, *10*, 1107–1117. [[CrossRef](#)]
79. Nakamura, T.; Mori, T.; Tada, S.; Krajewski, W.; Rozovskaia, T.; Wassell, R.; Dubois, G.; Mazo, A.; Croce, C.M.; Canaani, E. ALL-1 is a histone methyltransferase that assembles a supercomplex of proteins involved in transcriptional regulation. *Mol. Cell* **2002**, *10*, 1119–1128. [[CrossRef](#)]
80. Guccione, E.; Martinato, F.; Finocchiaro, G.; Luzi, L.; Tizzoni, L.; Dall' Olio, V.; Zardo, G.; Nervi, C.; Bernard, L.; Amati, B. Myc-binding-site recognition in the human genome is determined by chromatin context. *Nat. Cell Biol.* **2006**, *8*, 764–770. [[CrossRef](#)]
81. Kuvardina, O.N.; Herglotz, J.; Kolodziej, S.; Kohrs, N.; Herkt, S.; Wojcik, B.; Oellerich, T.; Corso, J.; Behrens, K.; Kumar, A.; et al. RUNX1 represses the erythroid gene expression program during megakaryocytic differentiation. *Blood* **2015**, *125*, 3570–3579. [[CrossRef](#)]
82. Stein, C.; Nötzold, R.R.; Riedl, S.; Bouchard, C.; Bauer, U.M. The arginine methyltransferase PRMT6 cooperates with polycomb proteins in regulating HOXA gene expression. *PLoS ONE* **2016**, *11*, e0148892. [[CrossRef](#)]
83. Dawson, D.W.; Pearce, S.F.A.; Zhong, R.; Silverstein, R.L.; Frazier, W.A.; Bouck, N.P. CD36 mediates the in vitro inhibitory effects of thrombospondin-1 on endothelial cells. *J. Cell Biol.* **1997**, *138*, 707–717. [[CrossRef](#)] [[PubMed](#)]
84. Dawson, D.W.; Volpert, O.V.; Frieda, S.; Schneider, A.J.; Silverstein, R.L.; Henkin, J.; Bouck, N.P. Three distinct D-amino acid substitutions confer potent antiangiogenic activity on an inactive peptide derived from a thrombospondin-1 type 1 repeat. *Mol. Pharmacol.* **1999**, *55*, 332–338. [[CrossRef](#)]
85. Michaud-Levesque, J.; Richard, S. Thrombospondin-1 is a transcriptional repression target of PRMT6. *J. Biol. Chem.* **2009**, *284*, 21338–21346. [[CrossRef](#)] [[PubMed](#)]
86. Kim, N.H.; Kim, S.N.; Seo, D.W.; Han, J.W.; Kim, Y.K. PRMT6 overexpression upregulates TSP-1 and downregulates MMPs: Its implication in motility and invasion. *Biochem. Biophys. Res. Commun.* **2013**, *432*, 60–65. [[CrossRef](#)]
87. Phalke, S.; Mzoughi, S.; Bezzi, M.; Jennifer, N.; Mok, W.C.; Low, D.H.P.; Thike, A.A.; Kuznetsov, V.A.; Tan, P.H.; Voorhoeve, P.M.; et al. P53-Independent regulation of p21Waf1/Cip1 expression and senescence by PRMT6. *Nucleic Acids Res.* **2012**, *40*, 9534–9542. [[CrossRef](#)] [[PubMed](#)]
88. Hwang, J.W.; So, Y.S.; Bae, G.U.; Kim, S.N.; Kim, Y.K. Protein arginine methyltransferase 6 suppresses adipogenic differentiation by repressing peroxisome proliferator-activated receptor γ activity. *Int. J. Mol. Med.* **2019**, *43*, 2462–2470. [[CrossRef](#)]
89. Dhawan, S.; Georgia, S.; Tschen, S.; Fan, G.; Bhushan, A. Pancreatic β Cell Identity Is Maintained by DNA Methylation-Mediated Repression of Arx. *Dev. Cell* **2011**, *20*, 419–429. [[CrossRef](#)] [[PubMed](#)]
90. Damez-Werno, D.M.; Sun, H.S.; Scobie, K.N.; Shao, N.; Rabkin, J.; Dias, C.; Calipari, E.S.; Maze, I.; Pena, C.J.; Walker, D.M.; et al. Histone arginine methylation in cocaine action in the nucleus accumbens. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 9623–9628. [[CrossRef](#)]
91. Herkt, S.C.; Kuvardina, O.N.; Herglotz, J.; Schneider, L.; Meyer, A.; Pommerenke, C.; Salinas-Riester, G.; Seifried, E.; Bonig, H.; Lausen, J. Protein arginine methyltransferase 6 controls erythroid gene expression and differentiation of human CD34+ progenitor cells. *Haematologica* **2018**, *103*, 18–29. [[CrossRef](#)]
92. Bostick, M.; Jong, K.K.; Estève, P.O.; Clark, A.; Pradhan, S.; Jacobsen, S.E. UHRF1 plays a role in maintaining DNA methylation in mammalian cells. *Science* **2007**, *317*, 1760–1764. [[CrossRef](#)]
93. Sharif, J.; Muto, M.; Takebayashi, S.I.; Suetake, I.; Iwamatsu, A.; Endo, T.A.; Shinga, J.; Mizutani-Koseki, Y.; Toyoda, T.; Okamura, K.; et al. The SRA protein Np95 mediates epigenetic inheritance by recruiting Dnmt1 to methylated DNA. *Nature* **2007**, *450*, 908–912. [[CrossRef](#)] [[PubMed](#)]
94. Lallous, N.; Legrand, P.; McEwen, A.G.; Ramón-Maiques, S.; Samama, J.P.; Birck, C. The PHD finger of human UHRF1 reveals a new subgroup of unmethylated histone H3 tail readers. *PLoS ONE* **2011**, *6*, e0027599. [[CrossRef](#)] [[PubMed](#)]
95. Wang, C.; Shen, J.; Yang, Z.; Chen, P.; Zhao, B.; Hu, W.; Lan, W.; Tong, X.; Wu, H.; Li, G.; et al. Structural basis for site-specific reading of unmodified R2 of histone H3 tail by UHRF1 PHD finger. *Cell Res.* **2011**, *21*, 1379–1382. [[CrossRef](#)]
96. Rajakumara, E.; Wang, Z.; Ma, H.; Hu, L.; Chen, H.; Lin, Y.; Guo, R.; Wu, F.; Li, H.; Lan, F.; et al. PHD Finger Recognition of Unmodified Histone H3R2 Links UHRF1 to Regulation of Euchromatic Gene Expression. *Mol. Cell* **2011**, *43*, 275–284. [[CrossRef](#)] [[PubMed](#)]
97. Hu, L.; Li, Z.; Wang, P.; Lin, Y.; Xu, Y. Crystal structure of PHD domain of UHRF1 and insights into recognition of unmodified histone H3 arginine residue 2. *Cell Res.* **2011**, *21*, 1374–1378. [[CrossRef](#)]
98. Schneider, L.; Herkt, S.; Wang, L.; Feld, C.; Wesely, J.; Kuvardina, O.N.; Meyer, A.; Oellerich, T.; Häupl, B.; Seifried, E.; et al. PRMT6 activates cyclin D1 expression in conjunction with the transcription factor LEF1. *Oncogenesis* **2021**, *10*, 42. [[CrossRef](#)]
99. Bouchard, C.; Sahu, P.; Meixner, M.; Nötzold, R.R.; Rust, M.B.; Kremmer, E.; Feederle, R.; Hart-Smith, G.; Finkernagel, F.; Bartkuhn, M.; et al. Genomic Location of PRMT6-Dependent H3R2 Methylation Is Linked to the Transcriptional Outcome of Associated Genes. *Cell Rep.* **2018**, *24*, 3339–3352. [[CrossRef](#)] [[PubMed](#)]

100. Sakabe, K.; Hart, G.W. O-GlcNAc transferase regulates mitotic chromatin dynamics. *J. Biol. Chem.* **2010**, *285*, 34460–34468. [[CrossRef](#)]
101. Miranda, T.B.; Webb, K.J.; Edberg, D.D.; Reeves, R.; Clarke, S. Protein arginine methyltransferase 6 specifically methylates the nonhistone chromatin protein HMGA1a. *Biochem. Biophys. Res. Commun.* **2005**, *336*, 831–835. [[CrossRef](#)]
102. Sgarra, R.; Lee, J.; Tessari, M.A.; Altamura, S.; Spolaore, B.; Giacotti, V.; Bedford, M.T.; Manfioletti, G. The AT-hook of the chromatin architectural transcription factor high mobility group A1a is arginine-methylated by protein arginine methyltransferase 6. *J. Biol. Chem.* **2006**, *281*, 3764–3772. [[CrossRef](#)]
103. Zou, Y.; Webb, K.; Perna, A.D.; Zhang, Q.; Clarke, S.; Wang, Y. A mass spectrometric study on the in vitro methylation of HMGA1a and HMGA1b proteins by PRMTs: Methylation specificity, the effect of binding to AT-rich duplex DNA, and the effect of C-terminal phosphorylation. *Biochemistry* **2007**, *46*, 7896–7906. [[CrossRef](#)] [[PubMed](#)]
104. Han, H.S.; Jung, C.Y.; Yoon, Y.S.; Choi, S.; Choi, D.; Kang, G.; Park, K.G.; Kim, S.T.; Koo, S.H. Arginine methylation of CRT2 is critical in the transcriptional control of hepatic glucose metabolism. *Sci. Signal.* **2014**, *7*, ra19. [[CrossRef](#)] [[PubMed](#)]
105. Huang, J.; Cardamone, M.D.; Johnson, H.E.; Neault, M.; Chan, M.; Floyd, Z.E.; Mallette, F.A.; Perissi, V. Exchange factor TBL1 and arginine methyltransferase PRMT6 cooperate in protecting g protein pathway suppressor 2 (GPS2) from proteasomal degradation. *J. Biol. Chem.* **2015**, *290*, 19044–19054. [[CrossRef](#)] [[PubMed](#)]
106. Yan, W.; Liang, Y.; Zhang, Q.; Wang, D.; Lei, M.; Qu, J.; He, X.; Lei, Q.; Wang, Y. Arginine methylation of SIRT 7 couples glucose sensing with mitochondrial biogenesis. *EMBO Rep.* **2018**, *19*, e46377. [[CrossRef](#)] [[PubMed](#)]
107. Choi, S.; Jeong, H.J.; Kim, H.; Choi, D.; Cho, S.C.; Seong, J.K.; Koo, S.H.; Kang, J.S. Skeletal muscle-specific Prmt1 deletion causes muscle atrophy via deregulation of the PRMT6-FOXO3 axis. *Autophagy* **2019**, *15*, 1069–1081. [[CrossRef](#)]
108. Migazzi, A.; Scaramuzzino, C.; Anderson, E.N.; Tripathy, D.; Hernández, I.H.; Grant, R.A.; Rocuzzo, M.; Tosatto, L.; Virlogeux, A.; Zuccato, C.; et al. Huntingtin-mediated axonal transport requires arginine methylation by PRMT6. *Cell Rep.* **2021**, *35*, 108980. [[CrossRef](#)]
109. Che, N.; Ng, K.Y.; Wong, T.L.; Tong, M.; Kau, P.W.; Chan, L.H.; Lee, T.K.; Huen, M.S.; Yun, J.P.; Ma, S. PRMT6 deficiency induces autophagy in hostile microenvironments of hepatocellular carcinoma tumors by regulating BAG5-associated HSC70 stability. *Cancer Lett.* **2021**, *501*, 247–262. [[CrossRef](#)] [[PubMed](#)]
110. Hübscher, U.; Maga, G.; Spadari, S. Eukaryotic DNA polymerases. *Annu. Rev. Biochem.* **2002**, *71*, 133–163. [[CrossRef](#)]
111. Idriss, H.T.; Al-Assar, O.; Wilson, S.H. DNA polymerase β . *Int. J. Biochem. Cell Biol.* **2002**, *34*, 321–324. [[CrossRef](#)]
112. Sobol, R.W.; Horton, J.K.; Kühn, R.; Gu, H.; Singhal, R.K.; Prasad, R.; Rajewsky, K.; Wilson, S.H. Requirement of mammalian DNA polymerase- β in base-excision repair. *Nature* **1996**, *379*, 183–186. [[CrossRef](#)]
113. Bustin, M. Regulation of DNA-Dependent Activities by the Functional Motifs of the High-Mobility-Group Chromosomal Proteins. *Mol. Cell. Biol.* **1999**, *19*, 5237–5246. [[CrossRef](#)]
114. Thanos, D.; Maniatis, T. Virus induction of human IFN β gene expression requires the assembly of an enhanceosome. *Cell* **1995**, *83*, 1091–1100. [[CrossRef](#)]
115. Reeves, R. Molecular biology of HMGA proteins: Hubs of nuclear function. *Gene* **2001**, *277*, 63–81. [[CrossRef](#)]
116. Yoshizawa, T.; Karim, M.F.; Sato, Y.; Senokuchi, T.; Miyata, K.; Fukuda, T.; Go, C.; Tasaki, M.; Uchimura, K.; Kadomatsu, T.; et al. SIRT7 controls hepatic lipid metabolism by regulating the ubiquitin-proteasome pathway. *Cell Metab.* **2014**, *19*, 712–721. [[CrossRef](#)] [[PubMed](#)]
117. Shin, J.; He, M.; Liu, Y.; Paredes, S.; Villanova, L.; Brown, K.; Qiu, X.; Nabavi, N.; Mohrin, M.; Wojnoonski, K.; et al. SIRT7 represses myc activity to suppress er stress and prevent fatty liver disease. *Cell Rep.* **2013**, *5*, 654–665. [[CrossRef](#)] [[PubMed](#)]
118. Mohrin, M.; Shin, J.; Liu, Y.; Brown, K.; Luo, H.; Xi, Y.; Haynes, C.M.; Chen, D. A mitochondrial UPR-mediated metabolic checkpoint regulates hematopoietic stem cell aging. *Science* **2015**, *347*, 1374–1377. [[CrossRef](#)] [[PubMed](#)]
119. Vazquez, B.N.; Thackray, J.K.; Simonet, N.G.; Kane-Goldsmith, N.; Martinez-Redondo, P.; Nguyen, T.; Bunting, S.; Vaquero, A.; Tischfield, J.A.; Serrano, L. SIRT 7 promotes genome integrity and modulates non-homologous end joining DNA repair. *EMBO J.* **2016**, *35*, 1488–1503. [[CrossRef](#)]
120. Barber, M.F.; Michishita-Kioi, E.; Xi, Y.; Tasselli, L.; Kioi, M.; Moqtaderi, Z.; Tennen, R.I.; Paredes, S.; Young, N.L.; Chen, K.; et al. SIRT7 links H3K18 deacetylation to maintenance of oncogenic transformation. *Nature* **2012**, *487*, 114–118. [[CrossRef](#)]
121. Chen, S.; Seiler, J.; Santiago-Reichert, M.; Felbel, K.; Grummt, I.; Voit, R. Repression of RNA Polymerase I upon Stress Is Caused by Inhibition of RNA-Dependent Deacetylation of PAF53 by SIRT7. *Mol. Cell* **2013**, *52*, 303–313. [[CrossRef](#)]
122. Quinn, P.G.; Granner, D.K. Cyclic AMP-dependent protein kinase regulates transcription of the phosphoenolpyruvate carboxykinase gene but not binding of nuclear factors to the cyclic AMP regulatory element. *Mol. Cell. Biol.* **1990**, *10*, 3357–3364. [[CrossRef](#)]
123. Montminy, M.; Koo, S.H.; Zhang, X. The CREB Family: Key regulators of hepatic metabolism. *Ann. Endocrinol. (Paris)* **2004**, *65*, 73–75. [[CrossRef](#)]
124. Koo, S.H.; Flechner, L.; Qi, L.; Zhang, X.; Sreaton, R.A.; Jeffries, S.; Hedrick, S.; Xu, W.; Boussouar, F.; Brindle, P.; et al. The CREB coactivator TORC2 is a key regulator of fasting glucose metabolism. *Nature* **2005**, *437*, 1109–1114. [[CrossRef](#)]
125. Herzig, S.; Long, F.; Jhala, U.S.; Hedrick, S.; Quinn, R.; Bauer, A.; Rudolph, D.; Schutz, G.; Yoon, C.; Puigserver, P.; et al. CREB regulates hepatic gluconeogenesis through the coactivator PGC-1. *Nature* **2001**, *413*, 179–183. [[CrossRef](#)] [[PubMed](#)]
126. Han, H.S.; Choi, D.; Choi, S.; Koo, S.H. Roles of protein arginine methyltransferases in the control of glucose metabolism. *Endocrinol. Metab.* **2014**, *29*, 435–440. [[CrossRef](#)] [[PubMed](#)]

127. Morris, B.J.; Willcox, D.C.; Donlon, T.A.; Willcox, B.J. FOXO3: A Major Gene for Human Longevity-A Mini-Review. *Gerontology* **2015**, *61*, 515–525. [[CrossRef](#)] [[PubMed](#)]
128. Moon, K.M.; Lee, M.-K.; Hwang, T.; Choi, C.W.; Kim, M.S.; Kim, H.-R.; Lee, B. The multi-functional roles of forkhead box protein O in skin aging and diseases. *Redox Biol.* **2021**, *46*, 102101. [[CrossRef](#)]
129. Sandri, M.; Sandri, C.; Gilbert, A.; Skurk, C.; Calabria, E.; Picard, A.; Walsh, K.; Schiaffino, S.; Lecker, S.H.; Goldberg, A.L. Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. *Cell* **2004**, *117*, 399–412. [[CrossRef](#)]
130. Lecker, S.H.; Jagoe, R.T.; Gilbert, A.; Gomes, M.; Baracos, V.; Bailey, J.; Price, S.R.; Mitch, W.E.; Goldberg, A.L. Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. *FASEB J.* **2004**, *18*, 39–51. [[CrossRef](#)]
131. Senf, S.M.; Dodd, S.L.; Judge, A.R. FOXO signaling is required for disuse muscle atrophy and is directly regulated by Hsp70. *Am. J. Physiol.-Cell Physiol.* **2010**, *298*, C45. [[CrossRef](#)]
132. Peng, Y.-C.; Kuo, F.; Breiding, D.E.; Wang, Y.-F.; Mansur, C.P.; Androphy, E.J. AMF1 (GPS2) Modulates p53 Transactivation. *Mol. Cell. Biol.* **2001**, *21*, 5913–5924. [[CrossRef](#)]
133. Peng, Y.-C.; Breiding, D.E.; Sverdrup, F.; Richard, J.; Androphy, E.J. AMF-1/Gps2 Binds p300 and Enhances Its Interaction with Papillomavirus E2 Proteins. *J. Virol.* **2000**, *74*, 5872–5879. [[CrossRef](#)] [[PubMed](#)]
134. Sanyal, S.; Bävner, A.; Haroniti, A.; Nilsson, L.M.; Lundåsen, T.; Rehnmark, S.; Witt, M.R.; Einarsson, C.; Talianidis, I.; Gustafsson, J.Å.; et al. Involvement of corepressor complex subunit GPS2 in transcriptional pathways governing human bile acid biosynthesis. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 15665–15670. [[CrossRef](#)] [[PubMed](#)]
135. Zhang, J.; Kalkum, M.; Chait, B.T.; Roeder, R.G. The N-CoR-HDAC3 nuclear receptor corepressor complex inhibits the JNK pathway through the integral subunit GPS2. *Mol. Cell* **2002**, *9*, 611–623. [[CrossRef](#)]
136. Jakobsson, T.; Venteclef, N.; Toresson, G.; Damdimopoulos, A.E.; Ehrlund, A.; Lou, X.; Sanyal, S.; Steffensen, K.R.; Gustafsson, J.Å.; Treuter, E. GPS2 Is Required for Cholesterol Efflux by Triggering Histone Demethylation, LXR Recruitment, and Coregulator Assembly at the ABCG1 Locus. *Mol. Cell* **2009**, *34*, 510–518. [[CrossRef](#)] [[PubMed](#)]
137. Cardamone, D.M.; Krones, A.; Tanasa, B.; Taylor, H.; Ricci, L.; Ohgi, K.A.; Glass, C.K.; Rosenfeld, M.G.; Perissi, V. A Protective Strategy against Hyperinflammatory Responses Requiring the Nontranscriptional Actions of GPS2. *Mol. Cell* **2012**, *46*, 91–104. [[CrossRef](#)]
138. Cardamone, M.D.; Tanasa, B.; Chan, M.; Cederquist, C.T.; Andricovich, J.; Rosenfeld, M.G.; Perissi, V. GPS2/KDM4A pioneering activity regulates promoter-specific recruitment of PPAR γ . *Cell Rep.* **2014**, *8*, 163–176. [[CrossRef](#)]
139. Pommier, Y.; Sun, Y.; Huang, S.Y.N.; Nitiss, J.L. Roles of eukaryotic topoisomerases in transcription, replication and genomic stability. *Nat. Rev. Mol. Cell Biol.* **2016**, *17*, 703–721. [[CrossRef](#)]
140. Baker, N.M.; Rajan, R.; Mondragón, A. Structural studies of type I topoisomerases. *Nucleic Acids Res.* **2009**, *37*, 693–701. [[CrossRef](#)]
141. Yang, Y.; McBride, K.M.; Hensley, S.; Lu, Y.; Chedin, F.; Bedford, M.T. Arginine Methylation Facilitates the Recruitment of TOP3B to Chromatin to Prevent R Loop Accumulation. *Mol. Cell* **2014**, *53*, 484–497. [[CrossRef](#)] [[PubMed](#)]
142. Yang, Y.; Lu, Y.; Espejo, A.; Wu, J.; Xu, W.; Liang, S.; Bedford, M.T. TDRD3 Is an Effector Molecule for Arginine-Methylated Histone Marks. *Mol. Cell* **2010**, *40*, 1016–1023. [[CrossRef](#)]
143. Li, J.; Yen, C.; Liaw, D.; Podsypanina, K.; Bose, S.; Wang, S.I.; Puc, J.; Miliareis, C.; Rodgers, L.; McCombie, R.; et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. *Science* **1997**, *275*, 1943–1947. [[CrossRef](#)] [[PubMed](#)]
144. Steck, P.A.; Pershouse, M.A.; Jasser, S.A.; Yung, W.K.A.; Lin, H.; Ligon, A.H.; Langford, L.A.; Baumgard, M.L.; Hattier, T.; Davis, T.; et al. Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. *Nat. Genet.* **1997**, *15*, 356–362. [[CrossRef](#)] [[PubMed](#)]
145. Sulis, M.L.; Parsons, R. PTEN: From pathology to biology. *Trends Cell Biol.* **2003**, *13*, 478–483. [[CrossRef](#)]
146. Hopkins, B.D.; Hodakoski, C.; Barrows, D.; Mense, S.M.; Parsons, R.E. PTEN function: The long and the short of it. *Trends Biochem. Sci.* **2014**, *39*, 183–190. [[CrossRef](#)]
147. Orr, H.T.; Zoghbi, H.Y. Trinucleotide repeat disorders. *Annu. Rev. Neurosci.* **2007**, *30*, 575–621. [[CrossRef](#)]
148. Katsuno, M.; Adachi, H.; Kume, A.; Li, M.; Nakagomi, Y.; Niwa, H.; Sang, C.; Kobayashi, Y.; Doyu, M.; Sobue, G. Testosterone reduction prevents phenotypic expression in a transgenic mouse model of spinal and bulbar muscular atrophy. *Neuron* **2002**, *35*, 843–854. [[CrossRef](#)]
149. Kennedy, W.R.; Alter, M.; Sung, J.H. Progressive proximal spinal and bulbar muscular atrophy of late onset: A sex-linked recessive trait. *Neurology* **1968**, *18*, 671–680. [[CrossRef](#)]
150. Spada, A.R.L.; Wilson, E.M.; Lubahn, D.B.; Harding, A.E.; Fischbeck, K.H. Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. *Nature* **1991**, *352*, 77–79. [[CrossRef](#)]
151. Saudou, F.; Humbert, S. The Biology of Huntingtin. *Neuron* **2016**, *89*, 910–926. [[CrossRef](#)] [[PubMed](#)]
152. Gauthier, L.R.; Charrin, B.C.; Borrell-Pagès, M.; Dompierre, J.P.; Rangone, H.; Cordelières, F.P.; De Mey, J.; MacDonald, M.E.; Lefsmann, V.; Humbert, S.; et al. Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. *Cell* **2004**, *118*, 127–138. [[CrossRef](#)]
153. Gunawardena, S.; Goldstein, L.S.B. Disruption of axonal transport and neuronal viability by amyloid precursor protein mutations in *Drosophila*. *Neuron* **2001**, *32*, 389–401. [[CrossRef](#)]

154. Gunawardena, S.; Her, L.S.; Bruschi, R.G.; Laymon, R.A.; Niesman, I.R.; Gordesky-Gold, B.; Sintasath, L.; Bonini, N.M.; Goldstein, L.S.B. Disruption of axonal transport by loss of huntingtin or expression of pathogenic polyQ proteins in *Drosophila*. *Neuron* **2003**, *40*, 25–40. [[CrossRef](#)]
155. Trushina, E.; Dyer, R.B.; Badger, J.D.; Ure, D.; Eide, L.; Tran, D.D.; Vrieze, B.T.; Legendre-Guillemain, V.; McPherson, P.S.; Mandavilli, B.S.; et al. Mutant Huntingtin Impairs Axonal Trafficking in Mammalian Neurons In Vivo and In Vitro. *Mol. Cell. Biol.* **2004**, *24*, 8195–8209. [[CrossRef](#)]
156. Liang, C.; Wainberg, M.A. The role of Tat in HIV-1 replication: An activator and/or a suppressor? *AIDS Rev.* **2002**, *4*, 41–49.
157. Kalland, K.H.; Szilvay, A.M.; Langhoff, E.; Haukenes, G. Subcellular distribution of human immunodeficiency virus type 1 Rev and colocalization of Rev with RNA splicing factors in a speckled pattern in the nucleoplasm. *J. Virol.* **1994**, *68*, 1475–1485. [[CrossRef](#)]
158. Meggio, F.; D'Agostino, D.M.; Ciminale, V.; Chieco-Bianchi, L.; Pinna, L.A. Phosphorylation of HIV-1 Rev protein: Implication of protein kinase CK2 and pro-directed kinases. *Biochem. Biophys. Res. Commun.* **1996**, *226*, 547–554. [[CrossRef](#)]
159. Fernandes, J.D.; Jayaraman, B.; Frankel, A.D. The HIV-1 Rev response element: An RNA scaffold that directs the cooperative assembly of a homo-oligomeric ribonucleoprotein complex. *RNA Biol.* **2012**, *9*, 6–11. [[CrossRef](#)] [[PubMed](#)]
160. Shubsda, M.F.; Paoletti, A.C.; Hudson, B.S.; Borer, P.N. Affinities of packaging domain loops in HIV-1 RNA for the nucleocapsid protein. *Biochemistry* **2002**, *41*, 5276–5282. [[CrossRef](#)] [[PubMed](#)]
161. Roldan, A.; Warren, O.U.; Russell, R.S.; Liang, C.; Wainberg, M.A. A HIV-1 minimal gag protein is superior to nucleocapsid at in vitro tRNA³Lys annealing and exhibits multimerization-induced inhibition of reverse transcription. *J. Biol. Chem.* **2005**, *280*, 17488–17496. [[CrossRef](#)]
162. De Rocquigny, H.; Gabus, C.; Vincent, A.; Fournie-Zaluski, M.C.; Roques, B.; Darlix, J.L. Viral RNA annealing activities of human immunodeficiency virus type 1 nucleocapsid protein require only peptide domains outside the zinc fingers. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 6472–6476. [[CrossRef](#)]
163. Cen, S.; Khorchid, A.; Gabor, J.; Rong, L.; Wainberg, M.A.; Kleiman, L. Roles of Pr55 gag and NCp7 in tRNA³Lys Genomic Placement and the Initiation Step of Reverse Transcription in Human Immunodeficiency Virus Type 1. *J. Virol.* **2000**, *74*, 10796–10800. [[CrossRef](#)] [[PubMed](#)]
164. Sakaguchi, K.; Zambrano, N.; Baldwin, E.T.; Shapiro, B.A.; Erickson, J.W.; Omichinski, J.G.; Clore, G.M.; Gronenborn, A.M.; Appella, E. Identification of a binding site for the human immunodeficiency virus type 1 nucleocapsid protein. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5219–5223. [[CrossRef](#)]
165. Amarasinghe, G.K.; De Guzman, R.N.; Turner, R.B.; Chancellor, K.J.; Wu, Z.R.; Summers, M.F. NMR structure of the HIV-1 nucleocapsid protein bound to stem-loop SL2 of the Ψ -RNA packaging signal. Implications for genome recognition. *J. Mol. Biol.* **2000**, *301*, 491–511. [[CrossRef](#)] [[PubMed](#)]
166. Maki, A.H.; Ozarowski, A.; Misra, A.; Urbaneja, M.A.; Casas-Finet, J.R. Phosphorescence and optically detected magnetic resonance of HIV-1 nucleocapsid protein complexes with stem-loop sequences of the genomic ψ -recognition element. *Biochemistry* **2001**, *40*, 1403–1412. [[CrossRef](#)] [[PubMed](#)]
167. Lischka, P.; Toth, Z.; Thomas, M.; Mueller, R.; Stamminger, T. The UL69 Transactivator Protein of Human Cytomegalovirus Interacts with DEXD/H-Box RNA Helicase UAP56 To Promote Cytoplasmic Accumulation of Unspliced RNA. *Mol. Cell. Biol.* **2006**, *26*, 1631–1643. [[CrossRef](#)]
168. Toth, Z.; Lischka, P.; Stamminger, T. RNA-binding of the human cytomegalovirus transactivator protein UL69, mediated by arginine-rich motifs, is not required for nuclear export of unspliced RNA. *Nucleic Acids Res.* **2006**, *34*, 1237–1249. [[CrossRef](#)]
169. Mann, M.; Zou, Y.; Chen, Y.; Brann, D.; Vadlamudi, R. PELP1 oncogenic functions involve alternative splicing via PRMT6. *Mol. Oncol.* **2014**, *8*, 389–400. [[CrossRef](#)]
170. Bao, J.; Di Lorenzo, A.; Lin, K.; Lu, Y.; Zhong, Y.; Sebastian, M.M.; Muller, W.J.; Yang, Y.; Bedford, M.T. Mouse models of overexpression reveal distinct oncogenic roles for different type I protein arginine methyltransferases. *Cancer Res.* **2019**, *79*, 21–32. [[CrossRef](#)]
171. Vieira, F.Q.; Costa-Pinheiro, P.; Ramalho-Carvalho, J.; Pereira, A.; Menezes, F.D.; Antunes, L.; Carneiro, I.; Oliveira, J.; Henrique, R.; Jerónimo, C. Deregulated expression of selected histone methylases and demethylases in prostate carcinoma. *Endocr. Relat. Cancer* **2014**, *21*, 51–61. [[CrossRef](#)] [[PubMed](#)]
172. Almeida-Rios, D.; Graça, I.; Vieira, F.Q.; Ramalho-Carvalho, J.; Pereira-Silva, E.; Martins, A.T.; Oliveira, J.; Gonçalves, C.S.; Costa, B.M.; Henrique, R.; et al. Histone methyltransferase PRMT6 plays an oncogenic role of in prostate cancer. *Oncotarget* **2016**, *7*, 53018–53028. [[CrossRef](#)] [[PubMed](#)]
173. Jiang, N.; Li, Q.L.; Pan, W.; Li, J.; Zhang, M.F.; Cao, T.; Su, S.G.; Shen, H. PRMT6 promotes endometrial cancer via AKT/mTOR signaling and indicates poor prognosis. *Int. J. Biochem. Cell Biol.* **2020**, *120*, 105681. [[CrossRef](#)]
174. Feng, Q.; Li, X.; Sun, W.; Sun, M.; Li, Z.; Sheng, H.; Xie, F.; Zhang, S.; Shan, C. Targeting G6PD reverses paclitaxel resistance in ovarian cancer by suppressing GSTP1. *Biochem. Pharmacol.* **2020**, *178*, 114092. [[CrossRef](#)] [[PubMed](#)]
175. Avasarala, S.; Wu, P.Y.; Khan, S.Q.; Yanlin, S.; Van Scoyk, M.; Bao, J.; Di Lorenzo, A.; David, O.; Bedford, M.T.; Gupta, V.; et al. PRMT6 promotes lung tumor progression via the alternate activation of tumor-associated macrophages. *Mol. Cancer Res.* **2020**, *18*, 166–178. [[CrossRef](#)] [[PubMed](#)]
176. Tang, J.; Meng, Q.; Shi, R.; Xu, Y. PRMT6 serves an oncogenic role in lung adenocarcinoma via regulating p18. *Mol. Med. Rep.* **2020**, *22*, 3161–3172. [[CrossRef](#)]

177. Pan, R.; Yu, H.; Dai, J.; Zhou, C.; Ying, X.; Zhong, J.; Zhao, J.; Zhang, Y.; Wu, B.; Mao, Y.; et al. Significant association of PRMT6 hypomethylation with colorectal cancer. *J. Clin. Lab. Anal.* **2018**, *32*, e22590. [[CrossRef](#)]
178. Lim, Y.; Yu, S.; Yun, J.A.; Do, I.G.; Cho, L.; Kim, Y.H.; Kim, H.C. The prognostic significance of protein arginine methyltransferase 6 expression in colon cancer. *Oncotarget* **2018**, *9*, 9010–9020. [[CrossRef](#)]
179. Luo, Y.; Xie, C.; Brocker, C.N.; Fan, J.; Wu, X.; Feng, L.; Wang, Q.; Zhao, J.; Lu, D.; Tandon, M.; et al. Intestinal PPAR α Protects Against Colon Carcinogenesis via Regulation of Methyltransferases DNMT1 and PRMT6. *Gastroenterology* **2019**, *157*, 744–759. [[CrossRef](#)]
180. Okuno, K.; Akiyama, Y.; Shimada, S.; Nakagawa, M.; Tanioka, T.; Inokuchi, M.; Yamaoka, S.; Kojima, K.; Tanaka, S. Asymmetric dimethylation at histone H3 arginine 2 by PRMT6 in gastric cancer progression. *Carcinogenesis* **2019**, *40*, 15–26. [[CrossRef](#)]
181. Hadjebi, O.; Casas-Terradellas, E.; Garcia-Gonzalo, F.R.; Rosa, J.L. The RCC1 superfamily: From genes, to function, to disease. *Biochim. Biophys. Acta-Mol. Cell Res.* **2008**, *1783*, 1467–1479. [[CrossRef](#)] [[PubMed](#)]
182. Clarke, P.R.; Zhang, C. Spatial and temporal coordination of mitosis by Ran GTPase. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 464–477. [[CrossRef](#)]
183. Clarke, P.R. Keep it focused: PRMT6 drives the localization of RCC1 to chromosomes to facilitate mitosis, cell proliferation, and tumorigenesis. *Mol. Cell* **2021**, *81*, 1128–1129. [[CrossRef](#)]
184. Lavoie, H.; Therrien, M. Regulation of RAF protein kinases in ERK signalling. *Nat. Rev. Mol. Cell Biol.* **2015**, *16*, 281–298. [[CrossRef](#)] [[PubMed](#)]
185. Wong, T.L.; Ng, K.Y.; Tan, K.V.; Chan, L.H.; Zhou, L.; Che, N.; Hoo, R.L.C.; Lee, T.K.; Richard, S.; Lo, C.M.; et al. CRAF Methylation by PRMT6 Regulates Aerobic Glycolysis-Driven Hepatocarcinogenesis via ERK-Dependent PKM2 Nuclear Relocalization and Activation. *Hepatology* **2020**, *71*, 1279–1296. [[CrossRef](#)] [[PubMed](#)]
186. Kabbage, M.; Dickman, M.B. The BAG proteins: A ubiquitous family of chaperone regulators. *Cell. Mol. Life Sci.* **2008**, *65*, 1390–1402. [[CrossRef](#)] [[PubMed](#)]
187. Kalia, S.K.; Lee, S.; Smith, P.D.; Liu, L.; Crocker, S.J.; Thorarinsdottir, T.E.; Glover, J.R.; Fon, E.A.; Park, D.S.; Lozano, A.M. BAG5 inhibits parkin and enhances dopaminergic neuron degeneration. *Neuron* **2004**, *44*, 931–945. [[CrossRef](#)]
188. Arakawa, A.; Handa, N.; Ohsawa, N.; Shida, M.; Kigawa, T.; Hayashi, F.; Shirouzu, M.; Yokoyama, S. The C-Terminal BAG Domain of BAG5 Induces Conformational Changes of the Hsp70 Nucleotide-Binding Domain for ADP-ATP Exchange. *Structure* **2010**, *18*, 309–319. [[CrossRef](#)]
189. Limm, K.; Ott, C.; Wallner, S.; Mueller, D.W.; Oefner, P.; Hellerbrand, C.; Bosserhoff, A.K. Dereglulation of protein methylation in melanoma. *Eur. J. Cancer* **2013**, *49*, 1305–1313. [[CrossRef](#)]
190. Mitchell, L.H.; Drew, A.E.; Ribich, S.A.; Rioux, N.; Swinger, K.K.; Jacques, S.L.; Lingaraj, T.; Boriack-Sjodin, P.A.; Waters, N.J.; Wigle, T.J.; et al. Aryl Pyrazoles as Potent Inhibitors of Arginine Methyltransferases: Identification of the First PRMT6 Tool Compound. *ACS Med. Chem. Lett.* **2015**, *6*, 655–659. [[CrossRef](#)]
191. Shen, Y.; Szewczyk, M.M.; Eram, M.S.; Smil, D.; Kaniskan, H.Ü.; Ferreira De Freitas, R.; Senisterra, G.; Li, F.; Schapira, M.; Brown, P.J.; et al. Discovery of a Potent, Selective, and Cell-Active Dual Inhibitor of Protein Arginine Methyltransferase 4 and Protein Arginine Methyltransferase 6. *J. Med. Chem.* **2016**, *59*, 9124–9139. [[CrossRef](#)] [[PubMed](#)]
192. Shen, Y.; Li, F.; Szewczyk, M.M.; Halabelian, L.; Park, K.S.; Chau, I.; Dong, A.; Zeng, H.; Chen, H.; Meng, F.; et al. Discovery of a First-in-Class Protein Arginine Methyltransferase 6 (PRMT6) Covalent Inhibitor. *J. Med. Chem.* **2020**, *63*, 5477–5487. [[CrossRef](#)] [[PubMed](#)]
193. Gong, S.; Maegawa, S.; Yang, Y.; Gopalakrishnan, V.; Zheng, G.; Cheng, D. Licochalcone A is a natural selective inhibitor of arginine methyltransferase 6. *Biochem. J.* **2021**, *478*, 389–406. [[CrossRef](#)] [[PubMed](#)]
194. Shen, Y.; Li, F.; Szewczyk, M.M.; Halabelian, L.; Chau, I.; Eram, M.S.; Dela Señá, C.; Park, K.S.; Meng, F.; Chen, H.; et al. A First-in-Class, Highly Selective and Cell-Active Allosteric Inhibitor of Protein Arginine Methyltransferase 6. *J. Med. Chem.* **2021**, *64*, 3697–3706. [[CrossRef](#)]