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REVIEW

The Influence of Arginine Methylation in Immunity and Inflammation

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Abstract: Exploration in the field of epigenetics has revealed that protein arginine methyltransferases (PRMTs) contribute to disease, and this has given way to the development of specific small molecule compounds that inhibit arginine methylation. Protein arginine methylation is known to regulate fundamental cellular processes, such as transcription; pre-mRNA splicing and other RNA processing mechanisms; signal transduction, including the anti-viral response; and cellular metabolism. PRMTs are also implicated in the regulation of physiological processes, including embryonic development, myogenesis, and the immune system. Finally, the dysregulation of PRMTs is apparent in cancer, neurodegeneration, muscular disorders, and during inflammation. Herein, we review the functions of PRMTs in immunity and inflammation. We also discuss recent progress with PRMTs regarding the modulation of gene expression related to T and B lymphocyte differentiation, germinal center dynamics, and anti-viral signaling responses, as well as the clinical relevance of using PRMT inhibitors alone or in combination with other drugs to treat cancer, immune, and inflammatory-related diseases.

Keywords: PRMTs, epigenetics, histones, arginine methylation, immune, inflammation

Arginine Methylation and Inflammation

Arginine methylation is a common post-translational modification in mammalian cells.[1] Protein arginine methyltransferases (PRMTs) are the primary enzymes responsible for catalyzing the formation of methylarginines in proteins. PRMTs catalyze the transfer of methyl groups from S-adenosylmethionine (SAM) to the ω-guanidino nitrogen atoms of arginines in proteins.[2] There are nine PRMTs with three separate types of activity.[3] Type I PRMTs (PRMT1, PRMT2, PRMT3, PRMT4 (herein referred to as CARM1 for co-activator-associated methyltransferase 1), PRMT6, and PRMT8) catalyze the formation of monomethylarginine (MMA) and asymmetric dimethylarginine (aDMA). Type II PRMTs (PRMT5 and PRMT9) catalyze the formation of MMA and symmetric dimethylarginine (sDMA). PRMT7 is the only known type III PRMT, and it catalyzes only the formation of MMA (Figure 1A). There are currently no known dedicated arginine demethylases,[3] in contrast to the known family of Jumonji (Jmj) C (JmjC) lysine demethylases (KDMs).[4] Therefore, arginine methylation is largely considered to be a long-lasting, as opposed to transient and reversible, post-translational modification. JmjD6 was wrongfully reported as an arginine demethylase as it is a hydroxylase for lysines.[5] KDM3A, KDM4E, and KDM5C, known histone methyl lysine demethylases, also possess the ability to demethylate methylarginines in vitro,[6] but whether this weak activity is of physiological relevance remains to be shown. The protein arginine deiminase (PAD) family may offer the possibility to reverse methylarginine by converting it to neutral citrulline,[7] however, monomethylarginine is a poorer substrate than unmodified arginine.[7] Thus, we still await identification of enzymes capable of reversing methylarginine to arginine. Without affecting charge, the addition of methyl groups sterically disrupts hydrogen bonding at affected guanidino nitrogen atoms influencing "reader" association such as Tudor, plant homeodomain (PHD), and WD40 domain-containing proteins.[8]

PRMTs play a significant role in gene regulation by methylating histone marks.[9] PRMT1-catalyzed H4R3me2a and CARM1-catalyzed H3R17me2a, H3R26me2a and H3R42me2a and PRMT5 mediated H3R2me2s are activating histone

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Figure 1 Type I, II, and III PRMTs mediate the methylation of arginine using S-adenosyl-methionine. (**A**) Type I protein arginine (Arg, R) methyltransferases (PRMTs) (PRMT1, PRMT2, PRMT3, CARM1, PRMT6, and PRMT8) catalyze the formation of monomethylarginine (Rme1, MMA) and asymmetric dimethylarginine (Rme2a, aDMA) by transferring methyl groups from S-adenosylmethionine (SAM) to the ω-guanidino nitrogen atoms of arginines in proteins. S-adenosylhomocysteine (SAH) is produced in each methyltransferase reaction. Type II PRMTs (PRMT5 and PRMT9) catalyze the formation of MMA and symmetric dimethylarginine (Rme2s, sDMA). PRMT7 is the only known type III PRMT, and it catalyzes the formation of only MMA. There are currently no known dedicated arginine demethylases. (**B**) PRMT1-catalyzed H4R3me2a and CARM1-catalyzed H3R17me2a, H3R26me2a, and H3R42me2a, and PRMT5 H3R2me2s are activating histone marks, while PRMT5-catalyzed H2AR3me2s, H4R3me2s, and H3R8me2s; PRMT6-catalyzed H3R2me2a; and CARM1-catalyzed H2AR29me2a are repressive histone marks.

marks, while PRMT5-catalyzed H2AR3me2s, H4R3me2s, and H3R8me2s; PRMT6-catalyzed H3R2me2a; and CARM1-catalyzed H2AR29me2a are repressive histone marks (Figure 1B). PRMTs also methylate many other substrates to modulate processes and pathways including pre-mRNA splicing, mRNA translation, cell signaling, and DNA damage pathways.[3] Many PRMTs favor the methylation of arginine/glycine-rich repeats (RGG/RG motifs) in proteins with the exceptions of CARM1 and PRMT7 that favor arginine/proline-rich repeats (PGM motifs) and RXR motifs, where X is any amino acid, respectively.[3]

Inflammation is a component of innate immunity, the body's primary protective response to infection. Pathogenic molecules such as lipopolysaccharides (LPS), double-stranded DNA (dsDNA), and single-stranded RNA (ssRNA) are recognized by pattern recognition receptors (PRRs) such as toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)/melanoma differentiation-associated protein 5 (MDA5), and cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS).[10] Stimulation of PRRs results in the activation of several signaling pathways, including nuclear factor kappa B (NF-κB), interferon (IFN) regulatory factor (IRF) 3 (IRF3), IRF7, and mitogen-activated protein kinase (MAPK), and subsequently the transcription of genes that encode proinflammatory IFNs and cytokines.[10] The NF-κB family consists of five structurally similar proteins (NF-κB1/p50, NF-κB2/p52, RelA/p65, RelB, and c-Rel) that assemble into functional hetero- and homodimers.[11] Briefly, canonical activation of the NF-κB pathway involves phosphorylation and activation of the inhibitor of kappa B (IκB) kinase (IKK) complex, followed by phosphorylation, ubiquitination, and degradation of IκB alpha (IκBα) to liberate and allow NF-κB dimers (typically, RelA/p65-NF-κB1/p50 and NF-κB1/p50-c-Rel) to translocate to the nucleus where they can bind to specific κB response elements and stimulate the expression of target genes.[11] B and T lymphocytes can also mediate inflammation as part of the body's adaptive immune system.[12] Acute inflammation requires constant stimulation to be maintained, while chronic inflammation arises during sustained inflammation and may lead to autoimmune diseases, such as asthma, systemic lupus erythematosus (SLE), acute graft-versus-host disease (aGVHD), ulcerative colitis, rheumatoid arthritis (RA), and multiple sclerosis (MS) (see below).[13–15] It is known that PRMTs are involved in mediating inflammation and, thus, their inhibition may be a promising strategy for the treatment of inflammatory and autoimmune diseases. This review will summarize the currently understood roles of PRMTs in modulating inflammation and the immune response.

PRMT1 in Inflammation

In mammalian cells, PRMT1 is the most active and prevalent type I PRMT.[16] It is known to function as a transcriptional co-activator, and it is responsible for the generation of the activation mark, H4R3me2a.[17] PRMT1 has also been shown to play roles in the DNA damage response pathway by methylating DNA damage proteins and in RNA metabolism by methylating RNA binding proteins (RBPs) (for review see[3]). PRMT1 has been recognized as a mediator of inflammation through its interaction with transcription factors and co-activators, including signal transducer and activator of transcription (STAT) proteins, NF-κB, and cyclic adenosine monophosphate (cAMP) response element binding protein (CREB)-binding protein (CBP)/p300-interacting trans-activator 2 (CITED2) (reviewed in[18]). PRMT1 has also been directly linked to the expression of cytokines and major histocompatibility complex (MHC)-related genes.[19] This next section will detail how PRMT1 regulates inflammation.

PRMT1 largely functions as a negative regulator of inflammation. Reintjes et al. 2016 showed that PRMT1 directly interacts and methylates the NF-κB subunit, RelA/p65, at R30 to suppress tumor necrosis factor (TNF)-alpha (TNF-α)-induced activation of NF-κB.[20] Asymmetric dimethylation of RelA/p65 at R30 interferes with the ability of NF-κB to function as a transcription factor (Figure 2A). Interestingly, depletion of PRMT1 using short hairpin RNA (shRNA) prevented the attenuation of NF-κB target gene expression, normally observed to occur within 4 hours of TNF-α stimulation.[20] Further, in response to cytokine interleukin (IL) 4 (IL-4) stimulation, PRMT1 and CARM1 were shown to function as co-activators of STAT5 for the upregulation of CITED2.[21] CITED2 negatively regulates NF-κB activation by binding the co-activator CBP/p300 in the nucleus and preventing its association with RelA/p65. This prevents RelA/p65 acetylation, required for its binding and stimulation of target *A20* and *IL-8* promoters.[22] Finally, arginine methylation was shown to play a role in post-transcriptional regulation of MHC-related genes. The use of MTA (5'-methylthioadenosine), now known to be a specific inhibitor of PRMT5,[23–25] was shown to suppress IFN-γ-induced expression of human leukocyte antigen (HLA) A (HLA-A).[26] Moreover, PRMT1 has been linked to the transcriptional repression of

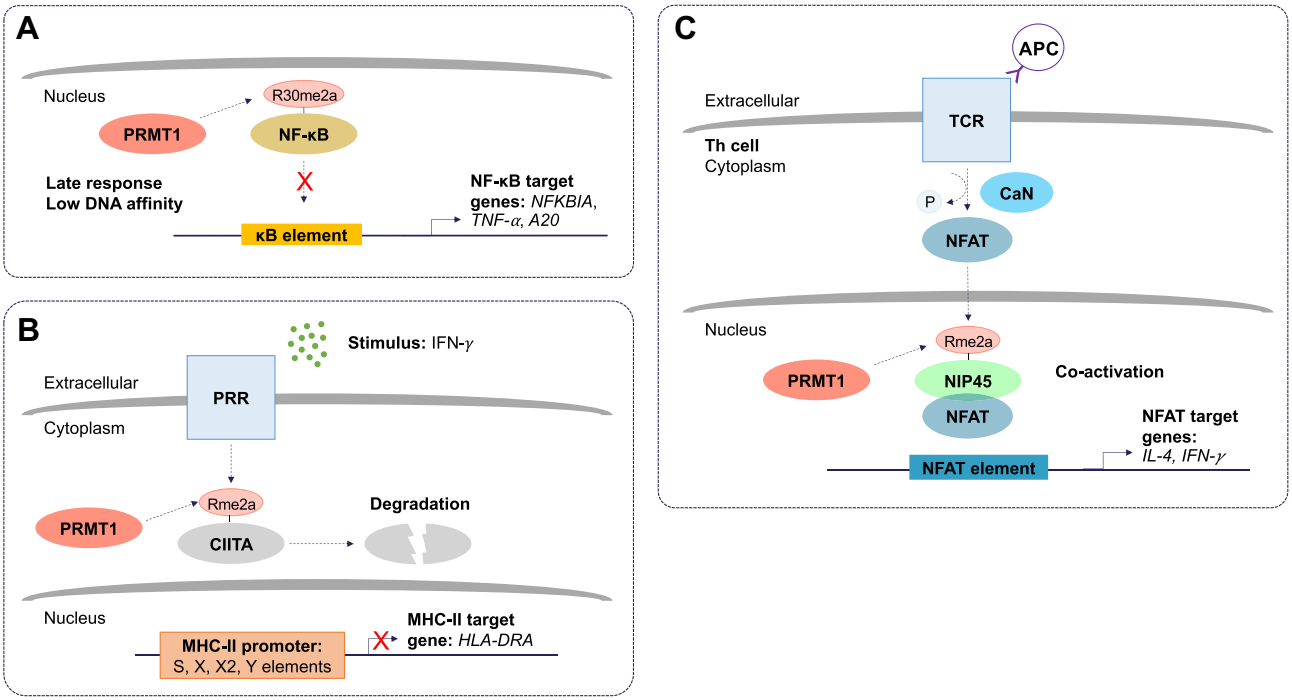


Figure 2 The molecular and cellular function of PRMT1 during inflammation. (**A**) Protein arginine methyltransferase 1 (PRMT1) negatively regulates the nuclear factor kappa B (NF-κB) pathway. Asymmetric dimethylation (Rme2a) of the NF-κB subunit, RelA/p65, at R30, reduces its ability to bind to kappa B (κB) sites with the consensus sequence 5'-GGGRNYYYCC-3', where R is an unspecified purine, Y is an unspecified pyrimidine, and N is any nucleotide. This prevents activation of promoters of NF-κB target genes. Asymmetric dimethylation of NF-κB is postulated to function as a late response in NF-κB activation. (**B**) PRMT1 suppresses class II trans-activator (CIITA)-mediated major histocompatibility complex II (MHC-II) transactivation. Pattern recognition receptor (PRR) stimulation by interferon-gamma (IFN-γ) results in asymmetric dimethylation of CIITA. This targets CIITA for degradation and prevents its translocation to the nucleus where it can stimulate the expression of MHC-II genes. (**C**) Asymmetric dimethylation of nuclear factor of activated T cells (NFAT)-interacting protein 45 kDa (NIP45) by PRMT1 positively regulates expression of NFAT target genes in T helper (Th) cells. T cell receptor (TCR) and antigen presenting cell (APC) ligation activates calcineurin (CaN). CaN dephosphorylates NFAT, allowing it to translocate to the nucleus. The interaction between NFAT and asymmetrically dimethylated NIP45 enhances the transcription of target genes.

hypoxia-inducible factor-1 alpha (HIF-1α) by regulating the activity of transcription factors, specificity protein (Sp) 1 (Sp1) and Sp3.[27] Depletion of PRMT1 using small interfering RNA (siRNA) was shown to increase HIF-1α levels and allow CREB to bind to the *HLA-B* promoter via chromatin remodeling.[28] These findings suggest a repressive epigenetic role for PRMT1 in the context of hypoxia, relevant especially to tumor-infiltrating monocytes. Additionally, PRMT1 was shown to methylate class II transactivator (CIITA) to promote its degradation and suppress IFN-γ-induced MHC-II transactivation in macrophages (Figure 2B).[19] PRMT1 silencing increased activity at the *MHC-II* promoter in the presence of IFN-γ and increased expression of HLA-DRA in both primary and transformed mouse peritoneal macrophages.[19] These findings provide a function for PRMT1 in vascular inflammation.

Conversely, arginine methylation of the N-terminal domain of nuclear factor of activated T cells (NFAT)-interacting protein (NIP45) by PRMT1, was found to be required for its interaction with NFAT and, thus, the activation of IL-4 and IFN-γ transcription in T helper (Th) 2 (Th2) and Th1 cells, respectively (Figure 2C).[29] NIP45 depletion prevents H4R3 methylation and H4 acetylation at relevant promoters, suggesting that PRMT1 can activate inflammation through histone methylation, but still primarily depends on non-histone methylation to initiate the response.[30] Significantly, it was shown that NIP45 deletion could ameliorate airway inflammation in asthma by decreasing type 2 innate lymphoid cells (ILC2) differentiation.[31] These data suggest that a PRMT1 inhibitor may only be useful to treat inflammation in selected contexts.

PRMT5 in Inflammation

PRMT5 generates the majority of cellular sDMA in mammalian cells. PRMT5 has many substrates (signaling molecules, RNA binding proteins, splicing factors, transcription factors, and histones) to regulate cellular processes (for review see[32]). Regulation by PRMT5 is critical for transcription; pre-mRNA and alternative splicing; signal transduction; and the DNA

damage response (for review see[3]). In this section, we will discuss how PRMT5 regulates the inflammatory response, particularly through the NF-κB pathway (Figure 3).

PRMT5 was originally cloned as a Janus kinase 2 (JAK2)-binding protein.[33] PRMT5 exists in a complex with methylosome protein 50 (MEP50) and a substrate adaptor protein (SAP), including pICln, RIO kinase 1 (RIOK1), and COPR5, to attract and methylate its substrates.[34] PRMT5 overwhelmingly serves as a positive regulator of inflammation. In a proteomic screen, PRMT5 was identified as a new TNF-related apoptosis-inducing ligand (TRAIL) receptor-binding protein.[35] Interestingly, PRMT5 contributes to TRAIL-induced activation of IKK and NF-κB, thus, leading to the induction of several NF-κB target genes.[36] Moreover, it was shown that PRMT5 gene silencing increased TRAIL-mediated cytotoxicity alone without affecting TNF-α-mediated NF-κB signaling. Another study reported that PRMT5-mediated methylation of homeobox A9 (HOXA9), a transcription factor for endothelial cell inflammatory responses, at R140 increased the level of endothelial-leukocyte adhesion molecule (ELAM).[37] Depletion of PRMT5 using siRNA led to a loss of E-selectin and vascular cell adhesion protein 1 (VCAM-1) induction, indicating that PRMT5 is an essential component for endothelial cell expression of leukocyte adhesion molecules during the inflammatory response. PRMT5 methylates the RelA/p65 subunit of NF-κB, promoting the expression of the proinflammatory chemokine, C-X-C motif chemokine ligand 10 (CXCL10), in response to TNF-α.[38] In addition, PRMT5-mediated methylation of RelA/p65 is required for CXCL11 induction during co-stimulation of

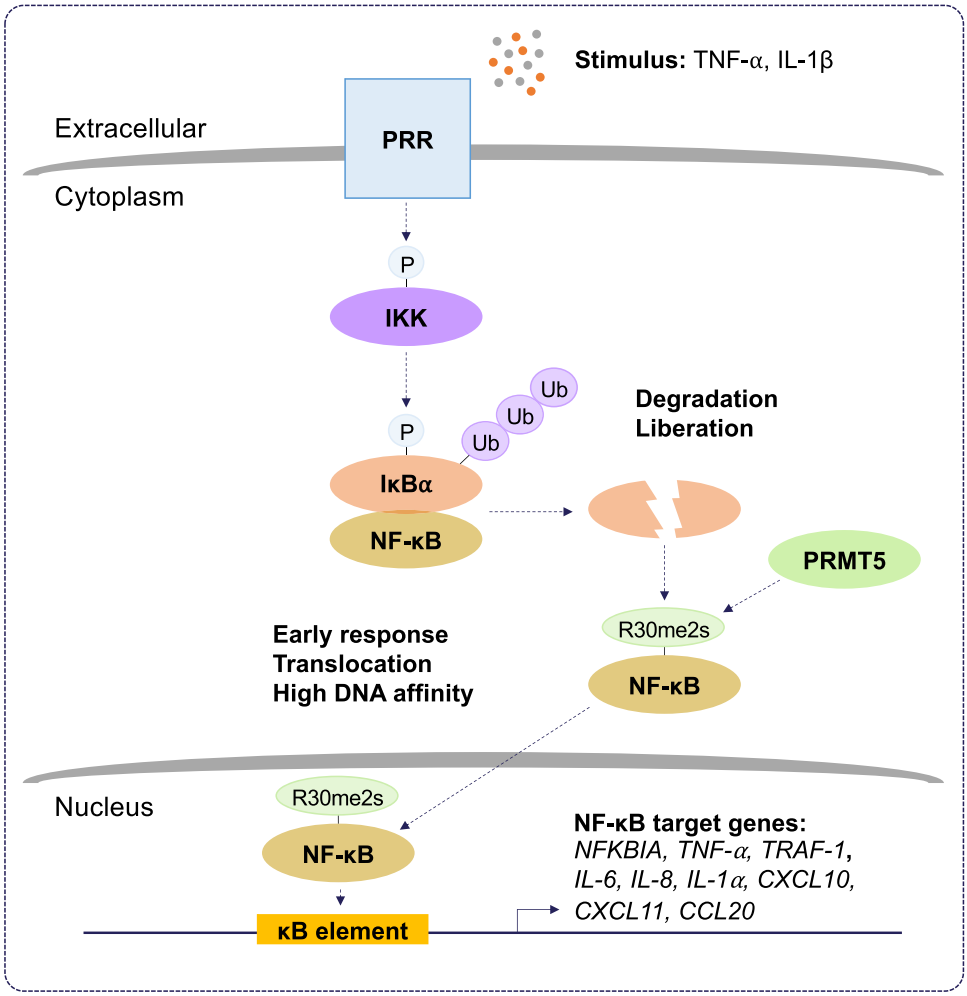


Figure 3 The role of PRMT5 during inflammation. Protein arginine methyltransferase 5 (PRMT5) positively regulates the nuclear factor kappa B (NF-κB) pathway. Pattern recognition receptor (PRR) stimulation by tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) results in the activation of inhibitor of kappa B (IκB) kinase (IKK). IKK activation leads to proteasomal degradation of IκB alpha (IκBα). This liberates NF-κB and allows PRMT5 to symmetrically dimethylate (Rme2s) the NF-κB subunit, RelA/p65, at R30. Symmetric dimethylation of NF-κB increases its affinity for kappa B (κB) sites with the consensus sequence 5'-GGGRNYYYCC-3', where R is an unspecified purine, Y is an unspecified pyrimidine, and N is any nucleotide, and this supports the activation of promoters regulating NF-κB target genes. Symmetric dimethylation of NF-κB is postulated to function as an early response in NF-κB activation.

endothelial cells with TNF-α and IFN-γ.[39] Interestingly, the methylation of RelA/p65 by PRMT5 at R30 increased its DNA binding activity and stimulated the expression of genes encoding cytokines, chemokines, and growth factors, including IL-1α, IL-8 and TNF receptor-associated factor 1 (TRAF-1).[40] Similar findings also indicate that PRMT5 regulates the NF-κB signaling through several cell membrane-bound receptors leading to the activation of the IKK complex.[41] It was shown that inhibition of PRMT5 methylation diminishes IKKβ and IKKα activation and RelA/p65 nuclear translocation.[41] Deletion of PRMT5 using siRNA and its pharmacological inhibition using EPZ015666 were shown to decrease the production of IL-6 and IL-8 and prevent cell proliferation, migration, and invasion by attenuating the activation of NF-κB.[41] Recently, PRMT5 was shown to increase VCAM-1 expression via symmetric dimethylation of RelA/p65 on R30.[42] PRMT5 knockdown in vascular smooth muscle cells (VSMCs) inhibited vascular inflammation and decreased VCAM-1 expression in mice. Together, these findings define a role for PRMT5 in the inflammatory response and suggest that the inhibition of PRMT5 might be an attractive therapeutic approach to attenuate pathological progression of inflammatory-related diseases.

Many different types of PRMT5 inhibitors have been generated. DS-437 was designed to occupy the SAM binding site and part of the substrate binding pocket of PRMT5 by adding a urea moiety that mimics the guanidinium group of substrate arginines to S-adenosylhomocysteine (SAH). Indeed, DS-437 prevented the methylation of histone H4 by PRMT5 but also was able to inhibit PRMT7; therefore, it is not specific for PRMT5.[43] EPZ015666 and GSK3203591 were designed as substrate competitive inhibitors of PRMT5.[44,45] These compounds are high-affinity inhibitors of SAM-bound PRMT5 complexes. As MTA was shown to be elevated in MTA phosphorylase (MTAP) negative cancers and to have preference for binding PRMT5,[23–25] a new specific inhibitor (MRTX1719) was generated that specifically inhibits the MTA-bound PRMT5-MEP50 complex.[46] Other strategies to inhibit PRMT5 include the development of a proteolysis-targeting chimeric (PROTAC) probe (MS4322) to degrade PRMT5.[47] Finally, another strategy has been to target the PRMT5 substrate adaptor interaction; BRD0639 disrupts the PRMT5-RIOK1 interactions required for the methylation of a variety of RIOK1-mediated, PRMT5-specific substrates.[48] The inhibitors referenced herein are listed in Table 1 (see below).

Type I PRMTs, PRMT6 and CARM1, also positively regulate inflammation. PRMT6 activates NF-κB by directly binding to RelA/p65 and promoting its nuclear translocation.[49] Using a gain-of-function PRMT6 allele in mice, it was shown that PRMT6 binds NF-κB-regulated promoters, such as *IL-6*, and stimulates gene expression upon TNF-α stimulation. CARM1 was also shown to interact directly with RelA/p65 and function as a co-activator at NF-κB target genes in response to TNF-α and LPS stimulation.[50] Further, CARM1 was found to participate in NF-κB-mediated transcription by remodeling chromatin via H3R17 methylation at inflammatory gene promoters such as *TNF-α, IL-8*, and *CXCL10* in monocytes.[51] Thus, given the prominent role of PRMTs in inflammation, it will be worthwhile to investigate whether certain PRMT inhibitors might enhance the effects of anti-inflammatory drugs.

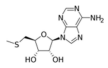
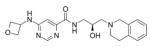
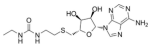
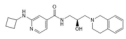
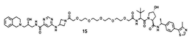
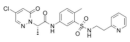
Physiological Role of PRMTs in the Immune System

Arginine methylation is a major contributor to immune development and function. Several PRMTs were shown to play a critical role in the establishment and maintenance of lymphoid and myeloid cell lines.[1,52] In the following section, the main functions of PRMTs in regulating the immune system will be discussed.

PRMT1 is known to affect T lymphocyte function. With the huge success of cancer immunotherapies and the generation of chimeric antigen receptor (CAR)-T cells, it becomes important to further understand the function of PRMT1 in T cells. Interestingly, PRMT1 was found to regulate the Th17 differentiation process.[53] PRMT1 interacts with growth factor independent 1 (GFI1), a transcriptional regulator required for development and maintenance of T lymphoid leukemia, to regulate the DNA damage response.[54] Moreover, PRMT1 is required for cytokine production by Th cells.[55]

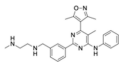
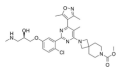
PRMT1 is also implicated in B lymphocyte regulation. In B cells, PRMT1 methylates cyclin-dependent kinase 4 (CDK4) and thereby prevents the formation of the CDK4-Cyclin-D3 complex and cell cycle progression. This methylation event blocks pre-B-cell proliferation and activates light chain immunoglobulin (IgL) gene assembly and pre-B-cell differentiation.[56] Furthermore, PRMT1 is necessary for lymphocyte development, proliferation, and differentiation in vivo.[57] PRMT1-deficient mice exhibit defects in B-cell development with diminished levels of serum antibodies by impairing T cell-independent antibody production. Arginine methylation of the Igα subunit of the B cell receptor (BCR) negatively regulates the calcium (Ca^{2+}) and the phosphatidylinositol 3-kinase (PI3K) signaling pathways of the BCR

Table 1 Defining Immune Function with PRMT Inhibitors

Compound	Mechanism of Action	PRMT Selectivity	In Vivo Activity	Reference
MTA 	SAM competitive	PRMT5	Suppresses IFN-γ-induced expression of HLA-A but not HLA-E in cancer cell lines	[23–26]
EPZ015666 	Substrate competitive	PRMT5	Attenuates NF-κB activation; suppresses activation of FLSs from RA patients; attenuates cartilage degeneration in OA mouse models; antitumor effect in MCL, AML, and TNBC mouse models	[41,44,45,140,141]
DS-437 	SAM and substrate competitive	PRMT5, PRMT7	Antitumoral effect when combined with $p185^{erbB2/neu}$ immunotherapy	[43,115]
GSK3203591 	Substrate competitive	PRMT5	Antitumoral effect in a MCL mouse model	[45]
MRTX1719 	PRMT5-MTA selective	PRMT5	Inhibits PRMT5 in MTAP negative cancer cells	[46]
MS4322 	PRMT5 PROTAC	PRMT5	Degrades PRMT5; antitumoral effect in multiple cancer cell lines	[47]
BRD0639 	PRMT5-binding motif competitive	PRMT5	Disrupts PRMT5- RIOK1 complexes; antitumoral effect in MTAP negative cancer cells	[48]
TP-064 	Substrate competitive	CARM1	Attenuates lymphocyte cell death in mice with sepsis	[67]

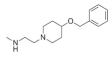
(*Continued*)

Table 1 (Continued).

Compound	Mechanism of Action	PRMT Selectivity	In Vivo Activity	Reference
HLCL65 	SAM competitive	PRMT5	Suppresses inflammation in a EAE mouse model	[96]
C220 	SAM competitive	PRMT5	Suppresses inflammation in an aGVHD mouse model	[98]
PT1001B 	Substrate competitive	Type I	Antitumoral effect when combined with an anti-PD-L1 checkpoint inhibitor in a PDAC mouse model	[108]
MS023 	Substrate competitive	Type I	Antitumoral effect when combined with an anti-PD-L1 checkpoint inhibitor in a colon cancer mouse model; anti-viral effect in SARS-CoV-2-infected cells	[109,133,137]
Compound 43 	Substrate competitive	CARM1	Antitumoral effect in TNBC and melanoma mouse models	[112]
EZM2303 	Substrate competitive	CARM1	Antitumoral effect in multiple myeloma and melanoma mouse models	[111,112]
SGC3027 	SAM competitive	PRMT7	Antitumoral effect when combined with anti-PD-1 and anti-CTLA-4 checkpoint inhibitors in a melanoma mouse model	[116]

(*Continued*)

Table 1 (Continued).

Compound	Mechanism of Action	PRMT Selectivity	In Vivo Activity	Reference
GSK3368715 	Substrate competitive	Type I	Antitumoral effect in pancreatic, breast, and renal cancer mouse models	[99]
MS049 	Substrate competitive	CARM1, PRMT6	Reduces aDMA in cells	[138]
EPZ020411 	Substrate competitive	PRMT6, PRMT1, PRMT8	Antitumoral effect in a GBM mouse model	[139,142]

Abbreviations: PRMT, protein arginine methyltransferase; SAM, S-adenosylmethionine; HLA, human leukocyte antigen; FLSs, fibroblast-like synoviocytes; RA, rheumatoid arthritis; OA, osteoarthritis; MCL, myeloid cell leukemia; AML, acute myeloid leukemia; TNBC, triple-negative breast cancer; MTA, 5'-methyl-thioadenosine; MTAP, MTA phosphorylase; PROTAC, proteolysis-targeting chimeric; EAE, experimental autoimmune encephalomyelitis; aGVHD, acute graft-versus-host disease; PD-L1, anti-programmed death ligand 1; PDAC, pancreatic ductal adenocarcinoma; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PD-1, programmed cell death protein 1; CTLA-4, cytotoxic T lymphocyte-associated protein 4; aDMA, asymmetric dimethylarginine; GBM, glioblastoma.

while promoting B cell differentiation.[58] PRMT1 deletion in mature B cells also results in reduced B cell activation and differentiation, thereby impairing humoral immunity in vivo.[59] Additionally, PRMT1 plays a critical role in IL-6 production in macrophages.[60]

CARM1 methylates the thymocyte cyclic AMP-regulated phosphoprotein (TARPP), a T cell-specific factor, at R650 and, thus, regulates the differentiation of early thymocyte progenitors.[61] Knockout of CARM1 reduces the cluster of differentiation (CD) 4 negative ($CD4^-$) $CD8^-$ T cell population in mice and blocks thymocyte developmental at the $CD44^+$ $CD25^-$ stage.[61,62] Moreover, inhibition of CARM1 in T cells greatly increases $CD8^+$ T cell accumulation in tumors and enhances antitumorgenicity.[63] Further, transcriptomic data shows that CARM1 deletion upregulates the expression of *TCF7* and *MYB*, key genes required for the maintenance and self-renewal of memory T cell populations.[64,65] CARM1 is also required for Th17 differentiation by opening chromatin at critical gene loci.[66] Precisely, CARM1 was shown to generate the activating mark, H3R17me2a, and prevent the deposition of the repressive mark, H3K9me3, at the *IL-17* locus, thus, leading to amplified *IL-17A* transcription and activation of the Th17 differentiation program.[66]

Little is known about the role of CARM1 during B cell development. However, a recent study has shown that CARM1 is implicated in lineage differentiation for both B and T cells.[67] LPS stimulation was found to increase CARM1 expression in B and T lymphocytes as well as monocytes that mediate caspase-3-dependent lymphocyte cell death.[67] Inhibition of CARM1 activity using TP-064 attenuated lymphocyte cell death and protected mice following LPS lung injury and polymicrobial sepsis.[67] Moreover, CARM1 was shown to downregulate microRNA (miRNA) 223 (miR-223) expression via the methylation of runt-related transcription factor 1 (RUNX1) at residue R223 and lead to the recruitment of double PHD finger 2 (DPF2) to repress myeloid differentiation.[68] Strikingly, CARM1 overexpression inhibited the differentiation of adult hematopoietic stem cells (HSCs) in culture, while CARM1 knockdown promoted their

differentiation.[68] In 2018, Nimer et al. also showed that CARM1 plays a critical role in myeloid leukemogenesis.[69] CARM1 depletion minimally impacted normal hematopoiesis but strongly impaired leukemogenesis by disrupting cell cycle progression, promoting myeloid differentiation, and inducing apoptosis.[69] Thus, CARM1 could be a potential therapeutic target for certain hematopoietic cancers.

PRMT5-mediated arginine methylation in activated T cells has been shown to be essential for the recruitment of transcription factors during cytokine gene expression. Depletion of PRMT5 in T lymphocytes impairs IL-2 gene expression.[70] Moreover, PRMT5 modulates T cell activation processes via the regulation of the transcription of IFN-induced cytokine genes,[71] and when deleted, PRMT5 decreases signaling via the γc-family of cytokines and reduces peripheral $CD4^+$ and $CD8^+$ T cell populations.[72] PRMT5 depletion in the $CD4^+$ Th cell compartment suppressed Th17 differentiation and protected mice from Th17-mediated diseases such as experimental autoimmune encephalomyelitis (EAE), a mouse model of autoimmune inflammatory diseases of the central nervous system (CNS) (see below).[73]

PRMT5 was shown to be essential for T cell survival and proliferation by maintaining cytokine signaling.[36] PRMT5 expression was also shown to be upregulated during human T cell leukemia virus type-1 (HTLV-1)-mediated T cell transformation, and its inhibition resulted in increased viral gene expression and decreased cellular proliferation.[74] Little is known about the role of PRMT5 in the physiological function of B lymphocytes, but it has been shown that PRMT5 mRNA levels, together with protein sDMA levels, are elevated in activated B cells.[75] Additionally, PRMT5 is markedly overexpressed in primary Epstein-Barr virus (EBV) lymphomas and lymphoblastoid cell lines.[76] Together, these data suggest that PRMT5 overexpression could be a marker of B cellular transformation.[76] It was shown that PRMT5 acts in a chromatin-wide repressive manner during B cell transformation via H4R3me2s and H3R8me2s.[77,78] Thus, it is likely that inhibiting PRMT5 would block the initiation and maintenance of EBV-driven B lymphocyte transformation and survival without affecting resting and activated B cells. Furthermore, deleting PRMT5 in all hematopoietic cells reduces pro- and pre-B cell differentiation and impairs T cell development, followed by defects in cytokine signaling,[79] suggesting that PRMT5 is required for B cell development in the bone marrow. PRMT5 was shown to play an important role in the regulation of antibody responses and germinal center (GC) dynamics during the development of B cells.[80] Further understanding of PRMT5 substrates following B and T cell activation is required to define the function of arginine methylation in regulating signaling during lymphopoiesis.

PRMT7 is an essential contributor to B cell lymphomagenesis. While PRMT7 B cell knockout mice survive into adulthood, the loss of PRMT7 reduces mature marginal zone B cell populations and increases native follicular B cell populations, thus, promoting GC formation and plasma cell differentiation.[81] Mechanistically, PRMT7 was shown to influence H4R3me2s at the *Bcl6* promoter and negatively regulate Bcl6 expression.[81] Furthermore, PRMT7-deficient B cell mice secrete low levels of immunoglobulins, IgG1 and IgA.[81] Although H4R3me2s is not a histone mark catalyzed by PRMT7, it was shown that PRMT7 monomethylates neighboring H4R17 to allosterically influence PRMT5-mediated H4R3me2s.[82] These findings suggest that PRMT7 mediated histone methylation may play a role in the onset and progression of B cell lymphomas. Further studies are required to fully understand the intersection of the activities of different PRMTs in the regulation of B cell development.

Collectively, these findings provide insight into the essential contribution of arginine methylation to B cell and T cell development and provide rationale for targeting PRMTs in different immune cell-related diseases, for example, B cell non-Hodgkin lymphomas. Although PRMTs were linked to malignant B cell survival and proliferation, the overall relevance of PRMT overexpression during the transformation process also remains unclear and requires further investigation.

PRMTs in Immune Diseases

Asthma

Several studies link PRMT1 to allergic asthma. PRMT1 is overexpressed in the lung tissue of antigen-induced pulmonary inflammation (AIPI) E3 rat models and mediates eosinophil recruitment into the lungs in response to IL-4 expression.[83,84] Raf kinase inhibitor protein (RKIP) and protein inhibitor of activated STAT1 (PIAS1) are reciprocally

expressed in epithelial and fibroblast cells and inhibit IL-1β/NF-κB and IL-4/STAT6-mediated PRMT1 expression, respectively.[85] More recently, it was shown that PRMT1 regulates processing of asthma-related miRNAs in lung epithelial cells.[86] PRMT1 is recruited, in complex with either STAT1 or RUNX1, to promote processing of miRNAs upregulated alongside PRMT1 in patients with asthma in response to transforming growth factor beta 1 (TGF-β1).[86] These findings suggest a role for PRMT1 in acute and chronic asthma in epithelial cells and fibroblasts. Furthermore, these findings have implications for the treatment of acute and chronic asthma as PRMT1 could serve as a specific therapeutic target.

Systemic Lupus Erythematosus

Elevated free aDMA levels are observed in the blood of patients with SLE.[87] Further, elevated aDMA levels correlates with higher incidence of cardiovascular disease in these patients.[86] Autoantibodies targeting the spliceosomal, RNA-binding Sm proteins are present in the serum of SLE patients.[88] These autoantibodies recognize the symmetrically dimethylated RGG/RG epitopes of Sm proteins and p80-coilin,[89] suggesting that inhibition of PRMTs may suppress some of their ability to induce autoimmune reactions.

Multiple Sclerosis

Citrullination of myelin basic protein (MBP) is a well-characterized post-translational modification required for myelin membrane stability. Increased citrullinated MBP is observed in patients with MS.[90] The monomethylation and symmetric dimethylation of MBP at R107 was shown to be catalyzed by PRMT5.[91,92] Early studies found that PRMT activity increases during the myelination phase of development and is a requirement for the formation of compact myelin in the CNS.[93,94] Further, the importance of MBP methylation was demonstrated when myelinolysis was found to be associated with disturbances in methionine biosynthesis.[95] Numerous animal and patient studies confirmed this observation and demonstrated that supplementation, particularly of vitamin B_{12}, could reverse the degeneration. The PRMT5 inhibitor, HLCL65, was shown to effectively suppress adaptive memory Th cell responses and reduce inflammation in an EAE mouse model.[96] PRMT5 depletion in $CD4^+$ T cells was shown to protect mice from Th17-mediated diseases.[73] These findings define a function for PRMT5 in Th cell expansion and its inhibition in inflammatory diseases caused by aberrant Th cell activity. A new study showed a correlation between EAE severity and PRMT5-mediated promotion of G_1/S cell cycle progression in $CD4^+$ cells.[97] These results corroborate the findings of Webb et al. 2020[73] and emphasize the importance PRMT5 inhibitors could have in suppressing Th cell expansion. The mechanism by which PRMT5 specifically promotes Th cell activity is not yet fully understood.

Acute Graft-Versus-Host Disease

The PRMT5 inhibitor, C220, can suppress T cell proliferation and cytokine production to alleviate the severity of aGVHD in mouse models having received hematopoietic cell transplants.[98] PRMT5 inhibition deregulated the phosphorylation of extracellular signal-regulated kinase (ERK) 1 (ERK1), ERK2, and STAT1.[98] Patients with lymphoma and acute myeloid leukemia (AML) who receive hematopoietic cell transplants may also benefit from the anti-tumoral activity of PRMT5 inhibitors.[99,100]

Ulcerative Colitis

The importance of arginine methylation in T lymphocytes is shown in ulcerative colitis.[101] Mechanistically, PRMT5 depletion was found to indirectly lead to a decrease in H3K27 lysine methylation and DNMT1 binding at the *Foxp3* promoter to support T regulatory (Treg) cell differentiation in ulcerative colitis patients as well as in clinical mouse models.[101] PRMT5 mediates crosstalk with histone lysine methylation as H3R2me2s/H3R8me2s is needed for optimal deposition of methyl groups at H3K27 by enhancer of zeste homolog 2 (EZH2)/polycomb repressive complex 2 (PRC2).[102] Thus, selective PRMT5 inhibition may be an effective therapeutic strategy to reduce intestinal inflammation.

Rheumatoid Arthritis

The PRMT5 inhibitor, EPZ015666, inhibits proliferation, migration, and invasion of fibroblast-like synoviocytes (FLSs) from patients with RA by effectively reducing interleukin expression via the NF-κB and Ak strain transforming (AKT) pathways.[41] These results demonstrate a unique role for PRMT5 in the context of RA and suggest that its specific inhibition may have therapeutic benefits for this autoimmune disease. Moreover, EPZ015666 attenuated cartilage degeneration in mouse models of osteoarthritis (OA).[103] Furthermore, they show that PRMT5 overexpression in chondrocytes leads to elevated expression of matrix degrading enzymes via activation of MAPK and NF-κB signaling pathways. These data support the notion that PRMT5 inhibitors could have therapeutic value in the treatment of RA. Finally, post-translational modifications are known to play an important role in altering the immunogenicity of synovial tissue proteins. Namely, citrullination of type II collagen, α-enolase, and fibrinogen have been identified in patients with RA.[104] Moreover, autoantibodies recognizing these citrullinated proteins have been found in the serum of patients with RA.[105] Autoantibodies against methylated arginine epitopes have not yet been identified in patients with RA, however, it was reported that these patients have elevated levels of circulating sDMA metabolite in their circulation.[106] These findings suggest that post-translational modifications may be a source of neoepitope production during inflammation.

PRMTs in Cancer Immunotherapy

PRMTs have recently been identified as regulators of cancer immunity. Here, we discuss the most recent advances involving arginine methylation in immune checkpoint pathways.

PRMT1

Deletion of PRMT1 using CRISPR-Cas9 sensitizes the colon adenocarcinoma cell line, MC38, to anti-programmed cell death protein-1 (PD-1) immunotherapy.[107] Inhibiting PRMT1 was shown to sensitize tumors to T cell-mediated killing by enhancing the apoptosis of cancer cells. Furthermore, transcriptomic analysis showed that PRMT1 knockout alters the expression of genes involved in T cell-mediated tumor apoptosis and in the production of cytokines and chemokines such as CCL7 and CCL9.[107] In the same context, the combination of a type I PRMT inhibitor, PT1001B, with anti-programmed death-ligand (PD-L) 1 (PD-L1) inhibition was shown to reduce pancreatic cancer progression by upregulating $CD8^+$ T cell infiltration into tumors.[108] PT1001B inhibits PD-L1 expression in cancer cells and enhances the induction of tumor cell apoptosis (Figure 4A).[108] C57BL/6J mice injected with MC38 tumor cells and treated with type I PRMT inhibitor, MS023, also exhibit anti-tumor immunity. MS023 significantly inhibits tumor growth and enhances the checkpoint blockade.[109] In human hepatocellular carcinoma (HCC), PRMT1 overexpression is associated with poor prognosis. Moreover, PRMT1 expression correlates with PD-L1 and PD-L2, suggesting that PRMT1 is an important regulator of immune checkpoint pathways in HCC.[110]

CARM1

A CRISPR-Cas9 screen identified that CARM1 deletion in the tumor enhances antitumoral immunity associated with an increase in $CD8^+$ T cell and dendritic cell infiltration.[63] CARM1 was identified as a negative regulator of tumor-specific T cells in the B16.F10 melanoma model. Another recent study has shown that inhibiting CARM1 with a chemical probe, compound 43 (a modified version of EZM2302),[111] inhibited solid tumor growth of triple negative breast cancer cell line, BT549, and the melanoma cell line, A375, as xenografts in BALB/c nude mice. Compound 43 and EZM2302 displayed similar pharmacokinetic parameters, but compound 43 has a longer half-life and a higher plasma concentration. Zhang et al. 2021 showed that compound 43 exhibits excellent metabolic stability and elicits antitumor efficacy by increasing the number of activated $CD8^+$ T cells, thereby regulating the immunosuppressive tumor microenvironment.[112] These observations suggest that the inhibition of CARM1 may be used to treat solid tumors and be beneficial for the enhancement of cancer immunotherapy.

Recently, Fedoriw et al. 2022 showed that inhibiting type I PRMTs in cancer cells promotes antitumor immune responses by increasing T cell infiltration into the tumor microenvironment and enhancing the cytotoxic activity of T cells.[113] Moreover, they showed that type I PRMT inhibitors increased the expression of interferon stimulated genes

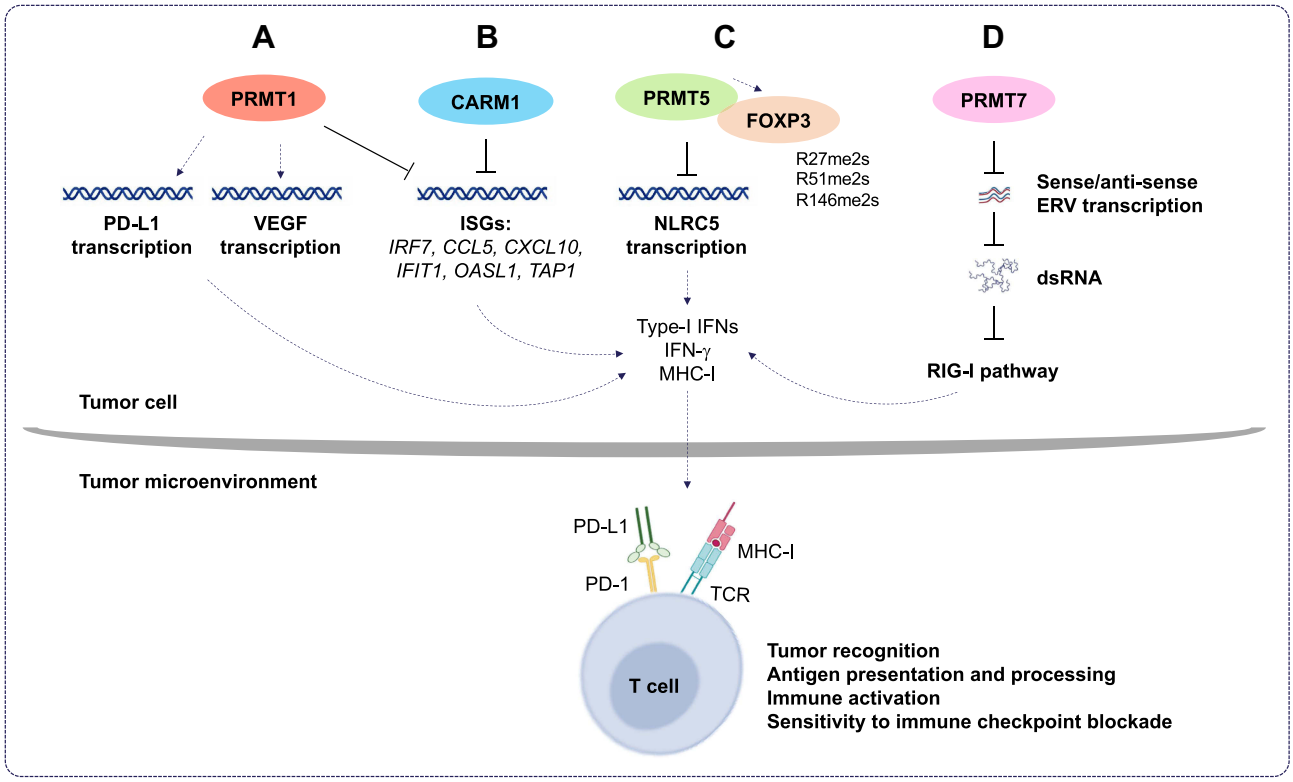


Figure 4 The roles of PRMT1, CARM1, PRMT5, and PRMT7 in cancer immunotherapy. (**A**) Protein arginine methyltransferase 1 (PRMT1) regulates programmed death-ligand 1 (PD-L1) expression in cancer cells and decreases tumor cell apoptosis. Also, PRMT1 induces the expression of the immunosuppressive factor, vascular endothelial growth factor (VEGF), and inhibits the expression of interferon (IFN) stimulates genes (ISGs). This, in turn, decreases the expression of several cytokines and chemokines and leads to immune checkpoint blockade resistance. (**B**) In tumor cells, co-activator-associated methyltransferase 1 (CARM1) inhibits ISG expression. This leads to inhibition of the type I IFN response and decreases the number of $CD8^+$ T cells in the tumor microenvironment. This increases the resistance of tumors cells to cancer immunotherapy. (**C**) Protein arginine methyltransferase 5 (PRMT5) promotes immunosuppression in cancer cells by inhibiting the transcription of NOD-like receptor (NLR)-family caspase activation and recruitment domain (CARD)-containing 5, which, in turn, modulates the expression of major histocompatibility complex I (MHC-I). This decreases antigen presentation and tumor recognition. Also, PRMT5 interacts directly with the transcription factor forkhead box P3 (FOXP3); dimethylates it at positions R27, R51, and R146; and suppresses T cells function. (**D**) Protein arginine methyltransferase 7 (PRMT7) maintains low expression of double-stranded RNA (dsRNA) repetitive elements that mimic viral induction of the retinoic acid-inducible gene I (RIG-I) pathway. This inhibits type I IFN and pro-inflammatory cytokine gene expression and decreases the sensitivity of tumors to the immune checkpoint blockade.
Abbreviations: Rme2s, symmetric dimethylarginine; ERVs, endogenous retroviral elements; PD-1, programmed cell death protein 1; TCR, T cell receptor.

(ISGs) via the cGAS/stimulator of interferon genes (STING) cytosolic DNA sensing pathway (Figure 4A and B). They also showed reduced expression of the immunosuppressive factor, vascular endothelial growth factor (VEGF) (Figure 4A).[113] Furthermore, combining type I PRMT inhibitors with immune checkpoint blockade enhanced the efficacy of cancer immunotherapy.[113]

PRMT5

PRMT5 has a pro-tumor intrinsic function as it promotes immunosuppression in melanoma mouse models. Notably, PRMT5 inhibition can potentiate immunotherapy by increasing IFN and chemokine production. It regulates the transcription of NOD-like receptor (NLR)-family caspase activation and recruitment domain (CARD)-containing 5 (NLRC5), a known regulator of the MHC-I antigen presentation pathway (Figure 4C).[114] PRMT5 methylates forkhead box P3 (FOXP3), a transcription factor known to regulate Treg development and function.[115] In this capacity, PRMT5 inhibition promotes tumor immunity by inhibiting Treg function and limiting Treg migration into tumors, thus, leading to enhancement of cancer immunotherapy and tumor-targeted therapies.

PRMT7

Recently, PRMT7 was identified as a new target to sensitize melanoma cells to cancer immunotherapy.[116] It was shown that combining anti-PD-1 and anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) therapy with PRMT7 deletion or PRMT7 inhibition using SGC3027, a cell permeable prodrug,[117] enhances anti-tumor responsiveness to the immune checkpoint blockade in a melanoma mouse model.[116] PRMT7-deficient B16.F10 melanoma cells exhibit increased dsRNA repetitive element expression, mimicking viral induction of the RIG-I pathway (Figure 4D). This induces type I IFNs and pro-inflammatory cytokines to enhance anti-tumoral immunity.[116]

In sum, the significance of PRMTs in the regulation of cancer immunity is gaining momentum and paving the way for future studies on the modulation and inhibition of arginine methylation for the treatment of solid tumors and to enhance the effectiveness of immune checkpoint blockade therapies.

PRMTs in Anti-Viral Responses

PRMTs are largely understood to negatively regulate the antiviral immune response.[3] In this section, we will discuss recent advances involving PRMTs in this response.

PRMT1 was shown to directly interact with TANK-binding kinase-1 (TBK1) and catalyze its methylation to promote TBK1 phosphorylation and activation for IFN production.[118] In contrast, type I PRMT inhibition in cancer cells stimulates IFN production,[113] suggesting that PRMT1 regulation of the anti-viral response maybe context-dependent and cell-type-specific. Thus, myeloid-specific PRMT1 knockout mice are more susceptible to viral infections due to their inability to activate TBK1 signaling.[118] Zebrafish PRMT3 and PRMT7 negatively regulate the antiviral response via IRF-3-mediated IFN production.[119,120] Mammalian PRMT7 was shown to negatively regulate the antiviral response through the monomethylation of mitochondrial antiviral signaling protein (MAVS) and, thus, the RIG-I-like receptor (RLR) signaling pathway.[121] PRMT5-mediated methylation of cGAS was also shown to abolish its DNA binding ability and attenuate the antiviral response via the cGAS/STING cytosolic DNA sensing pathway.[114,122] PRMT5 additionally regulates the cGAS/STING pathway by methylating one of its components, the IFN-γ-inducible protein 16 (IFI16).[114] Finally, it was shown that nuclear cGAS recruits PRMT5 and facilitates H3R2 methylation at the promoters of type I IFN genes, in turn enhancing antiviral immunity upon infection.[123] Another study showed that PRMT5 activates the transcription of type I and type III IFNs, IFNβ1 and IFNλ1, via the induction of the activating transcription factor 2 (ATF2), c-Jun, and TBK1.[71] Finally, PRMT6 was identified as a negative regulator of the TBK1-IRF3 signaling cascade attenuating the antiviral immune response.[124,125]

Arginine Methylation During Viral Infections

During viral infection both host and viral proteins are targets of PRMTs and their methylation has a profound influence on viral replication. PRMT6 was found to restrict human immunodeficiency virus (HIV) replication via the methylation of the HIV trans-activator (Tat) protein.[126] Subsequent studies suggest that arginine methylation suppresses Tat-mediated transactivation by preventing its nucleolar retention and proteasomal degradation.[127,128] Further, PRMT6 was found to methylate the HIV nucleocapsid protein and inhibit viral transcription.[129] PRMT5 and PRMT7 were discovered to similarly support HIV replication via maintenance of viral protein R (Vpr) stability.[130] Recently, inhibition of PRMT5 using EPZ015666 was shown to increase HIV internal ribosome entry site (IRES) activity via the loss of methylation of heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1).[131] PRMT5 has been shown to methylate the C-terminal domain of hepatitis B virus (HBV) core (HBc) protein and repress viral replication and transcription.[132] Certain viruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and EBV may benefit from PRMT inhibition. Briefly, the SARS-CoV-2 nucleocapsid (N) protein was recently shown to be methylated by PRMT1.[133] Interestingly, PRMT1 depletion or inhibition using MS023 was found to interfere with the ability of the N protein to localize to stress granules and bind to the 5'-UTR of SARS-CoV-2 RNA.[133] Furthermore, MS023 was shown to reduce SARS-CoV-2 replication in VeroE6 cells.[133] Finally, PRMT5 activity is understood to play a crucial role in Epstein-Barr nuclear antigen (EBNA) 1 (EBNA1)-mediated viral replication, EBNA2-mediated transcription, and EBV-dependent B cell immortalization.[134] Thus, PRMT5 inhibition might prove to be an effective therapeutic strategy in the treatment of EBV.

Although accumulating evidence implicates PRMTs in the modulation of anti-viral immunity, the underlying mechanisms by which arginine methylation regulates the antiviral immune response is not fully understood. Continued investigation will reveal these mechanisms and aid in developing more effective anti-viral treatments and diagnostic tools.

PRMT Inhibitors in the Treatment of Immune and Inflammatory-Related Diseases

There are several small molecule PRMT inhibitors currently in clinical trials for the treatment of cancer (for review see[3]). This is not surprising considering the numerous roles that PRMTs play in the regulation of cancer, the immune system, and anti-viral and inflammatory responses. PRMT inhibitors are therefore attractive therapeutic targets, particularly in lymphomas and leukemias where their expression is elevated.

A first-in-class PRMT5 degrader, MS4322, using PROTAC, has been developed.[47] MS4322 effectively degrades PRMT5 in an E3 ligase- and proteasome-dependent manner in mammalian cells.[47] Another approach has been to block the PRMT5-substrate adaptor interaction with first-in-class PRMT5 binding motif (PBM)-competitive small molecule, BRD0639. This inhibitor was shown to effectively outcompete binding between PRMT5 and RIOK1, inhibiting the methylation of certain PRMT5 substrates dependent on RIOK1 interaction.[135] A new potent and selective PRMT5 inhibitor that binds to the MTA-bound PRMT5 complex has also been developed. MRTX1719 has been shown to inhibit PRMT5 activity exclusively in MTAP negative cells.[46] This compound allows for selective targeting of only MTA-bound PRMT5 in MTAP negative cancer cells.

Several PRMT inhibitors target more than one PRMT.[136] For example, MS023 and GSK3368715 are both general type I PRMT inhibitors.[99,137] While MS049 targets both CARM1 and PRMT6, and DS-437 is a dual PRMT5 and PRMT7 inhibitor.[43,138] Finally, EPZ020411 has a higher affinity for PRMT6, but can also inhibit PRMT1 and PRMT8.[139] We summarize the main features of small-molecule PRMT inhibitors discussed herein as well as those that have been investigated in the context of immune and inflammatory-related diseases in Table 1.

Conclusions and Future Perspectives

As discussed in this review, arginine methylation plays an essential role in regulating inflammation, immunity, and antiviral responses, in particular, by modulating the activity of NF-κB. Although more detailed analyses are required, multiple studies propose that PRMTs can be targeted to improve inflammatory-related diseases, as well as leukemias and lymphomas. The development of drugs targeting the activity of PRMTs has gained significant momentum in the last several years, and the inclusion of PRMT inhibitors in current clinical trials warrants continued research on arginine methylation. The prospect of using PRMT inhibitors as anti-inflammatory and/or anti-viral, besides their use as potential cancer therapeutics, is promising.

Disclosure

The authors report no conflicts of interest in this work.

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