Involvement of SAMHD1 in dNTP homeostasis and the maintenance of genomic integrity and oncotherapy (Review)

ZHOU ZHANG[1,2], LIXIA ZHENG[1,2], YANG YU[1,2], JINYING WU[1,2], FAN YANG[1,3], YINGXI XU[1,3], QIQIANG GUO[1,2], XUAN WU[1,2], SUNRUN CAO[1,2], LIU CAO[1,2] and XIAOYU SONG[1,2]

[1]College of Basic Medical Science, Institute of Translational Medicine, China Medical University, Shenyang, Liaoning 110122; [2]Liaoning Province Collaborative Innovation Center of Aging Related Disease Diagnosis and Treatment and Prevention, Shenyang, Liaoning 110000; [3]Digestive Department, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110122, P.R. China

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Abstract. Sterile alpha motif and histidine/aspartic acid domain-containing protein 1 (SAMHD1), the only deoxynucleotide triphosphate (dNTP) hydrolase in eukaryotes, plays a crucial role in regulating the dynamic balance and ratio of cellular dNTP pools. Furthermore, SAMHD1 has been reported to be involved in the pathological process of several diseases. Homozygous *SAMHD1* mutations have been identified in immune system disorders, such as autoimmune disease Aicardi-Goutières syndrome (AGS), whose primary pathogenesis is associated with the abnormal accumulation and disproportion of dNTPs. SAMHD1 is also considered to be an intrinsic virus-restriction factor by suppressing the viral infection process, including reverse transcription, replication, packaging and transmission. In addition, SAMHD1 has been shown to promote genome integrity during homologous recombination following DNA damage, thus being considered a promising candidate for oncotherapy applications. The present review summarizes the molecular mechanisms of SAMHD1 regarding the regulation of dNTP homeostasis and DNA damage response. Additionally, its potential effects on tumorigenesis and oncotherapy are reported.

Correspondence to: Dr Xiaoyu Song or Dr Liu Cao, College of Basic Medical Science, Institute of Translational Medicine, China Medical University, 77 Puhe Road, Shenyang, Liaoning 110122, P.R. China
E-mail: xysong@cmu.edu.cn
E-mail: lcao@cmu.edu.cn

Abbreviations: AGS, Aicardi-Goutières syndrome; ARD1, acetyltransferase arrest defective protein 1; BIV, bovine immunodeficiency virus; B-MLV, B-tropic murine leukemia virus; CDK1, cyclin-dependent kinase 1; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T cell lymphoma; CTIP, c-terminal binding protein interacting protein; DDR, DNA damage response; dNTP, deoxynucleotide triphosphate; DSBs, DNA double-strand breaks; EBV, Epstein-Barr virus; EIAV, equine infectious anemia virus; FIV, feline immunodeficiency virus; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HIV, human immunodeficiency virus; HR, homologous recombination; HSV, herpes simplex virus; IFN-γ, interferon γ; N-MLV, N-tropic murine leukemia virus; RNase, ribonuclease; SAMHD1, sterile alpha motif and histidine-aspartic acid domain-containing protein 1; SIVs, simian immunodeficiency viruses; Vpr, viral protein R; Vpx, viral protein X; 53BP1, p53-binding protein 1

Key words: SAMHD1, dNTP hydrolase, genome integrity, DNA damage response, tumorigenesis

Contents

1. Introduction

Deoxynucleotide triphosphates (dNTPs) are the raw materials for DNA replication and repair, rendering them indispensable components for transmitting genetic information in cells and maintaining genomic stability (1,2). Sterile alpha motif and histidine/aspartic acid domain-containing protein 1 (SAMHD1), the only dNTP hydrolase in eukaryotes, is involved in several pathological processes. SAMHD1 is well known for its vital role in the resistance to virus transcription and replication by limiting the volume of the dNTP pool, thus resulting in the protection of the host cellular genome integrity. It has been reported that SAMHD1 acetylation enhances its dNTP hydrolase (dNTPase) activity and regulates cancer cell proliferation (3). Moreobver, the dNTPase activity of SAMHD1 is dependent on the stability of the catalytic core tetramer, which can be inhibited by cyclin-dependent kinase phosphorylation on threonine 592 (T592) (4-8). In addition, viral protein

kinases can also phosphorylate SAMHD1, thereby inhibiting its dNTPase activity (9,10). The transcriptional repression of *Samhd1* is mediated by methylation of its promoter (11-13). It has been also reported that viral protein X (Vpx) interacts with SAMHD1, resulting in the proteasomal degradation of SAMHD1 and an increase in dNTP levels (14-17). Therefore, it is necessary to systematically summarize the modifications of SAMHD1 and reveal its related downstream functions.

In the present review, the current knowledge of the role of SAMHD1 in the dynamic regulation of dNTP cellular homeostasis and genomic stability is summarized. In addition, the potential role of SAMHD1 as a housekeeping protein in the maintenance of dNTP homeostasis and the prevention of tumorigenesis is discussed.

2. Overview of SAMHD1

The human *SAMHD1* gene was first cloned in 2000 by Li *et al* via a human dendritic cell cDNA library (18) and it was identified as an effective interferon γ (IFN-γ)-induced protein (18,19). Based on its dNTPase activity, SAMHD1 is recognized as an intrinsic host restriction factor against human immunodeficiency virus 1 (HIV-1) (20). Additionally, *SAMHD1* is also known as the *AGS* gene. Multipoint mutations in *AGS* induce severe familial autoimmune Aicardi-Goutières syndrome (AGS) (21-24).

Human SAMHD1 is 626 amino acids (aa) in length and contains an N-terminal nuclear localization domain ^{11}KRPR^{14} followed by a conserved sterile alpha motif (SAM) and a histidine/aspartic acid (HD) domain (25,26). These domains are connected by a short linker and flanked by unstructured regions. The SAM domain (44-110 aa) is involved in protein-protein and protein-DNA/RNA interactions, whereas the HD domain is a conserved sequence containing 160-339 aa comprising an arrangement of alternating histidine/aspartic acid amino acids (27-29) (Fig. 1). HD is the main functional domain of SAMHD1 with antiviral activity, which is involved in nucleotide metabolism and exhibits dNTPase and ribonuclease (RNase) activity. However, the RNase activity of SAMHD1 is controversial. Ryoo *et al* (31) suggested that SAMHD1 restricted HIV-1 infection by cleaving the viral RNA genome via its RNase activity. In addition, the SAMHD1 phosphorylation at T592 negatively regulates its RNase activity *in vivo* and impedes HIV-1 restriction. By contrast, Antonucci *et al* (30) reported that SAMHD1 did not exhibit broad nuclease activity; however, they did not rule out a specific nucleolytic interaction between SAMHD1 and incoming HIV-1 genomic RNA (gRNA). Furthermore, Antonucci *et al* (30) demonstrated that both $SAMHD1_{D137N}$ (RNase-positive and dNTPase-negative) and $SAMHD1_{Q548A}$ (RNase-negative and dNTPase-positive) mutants were expressed at comparable levels with wild-type SAMHD1 and each efficiently restricted HIV-1 infection (30,31). Several studies have demonstrated that the C-terminus of SAMHD1 (600-626 aa) is included in the crystal structure of the GTP/dNTP-bound tetramer and forms a short alpha-helical structure with an extended loop (32-34). The C-terminus of SAMHD1 is required for the efficient depletion of dNTP pools and the inhibition of HIV-1 infection in monocytes (35). Although the C-terminal region contains conserved amino acid sequences, it extends interspersed with more divergent ones among vertebrate species (17). A recent study demonstrated that SAMHD1 catalytic activity is regulated by redox signaling. SAMHD1 is inactivated in a dose-dependent, yet reversible manner when treated with the oxidizing agent, H_2O_2 (36).

The oxidation of SAMHD1 has been demonstrated to inhibit tetramerization, and has been emphasized as a central regulatory mechanism for the regulation of SAMHD1 activity *in vivo* (37). Recent research has highlighted that rapid protein degradation is not mediated by SAMHD1 phosphorylation at T592. In addition, it has been documented that the dNTPase activity of SAMHD1 is not only retained during the G1 and G0 phases, but throughout the entire cell cycle, independent of phosphorylation at T592 (38). Other researchers have indicated that constructed mutant SAMHD1 fragments generated by deleting the HD domain and C-terminal segment inhibit the ability to restrict HIV-1 infection (39). In the absence of the dGTP co-factor, SAMHD1 exists as an inactive monomer or dimer in which the substrate-binding pocket is unable to bind dNTP, thus losing its dNTPase activity (27,35). Upon dGTP-Mg^{2+}-dGTP binding at the allosteric sites, the catalytically inactive SAMHD1 dimers tetramerize, thereby inducing a large conformational change at the tetramer interface and the recovery of its catalytic activity. Therefore, the dNTPase activity of SAMHD1 is mainly dependent on its active tetramer structure (35,40). Taken together, the aforementioned features of SAMHD1 verify its ability to properly regulate dNTP levels, which are indispensable for the transcription and replication of viruses, such as herpes simplex virus (HSV) type 1 (41,42) and hepatitis B virus (HBV) (43,44), and the inhibition of HIV-1 reverse transcription. The structure of SAMHD1 forms the basis of its biological functions and may thus provide novel insight into the elucidatation of the internal regulatory mechanisms of immune disorders, viral infections, DNA damage responses and tumorigenesis (45).

3. Modifications of SAMHD1

SAMHD1 is subjected to a vast array of post-translational modifications, including phosphorylation, acetylation and methylation. It has been suggested that cyclin-dependent kinase 1 (CDK1)/cyclin A2 phosphorylates SAMHD1 at T592 only in proliferating cells and completely abolish its ability to resist viral infections (46). In addition, SAMHD1 has been shown to be phosphorylated at T592 in proliferating leukocytes in the G1/S and G2/M phase of the cell cycle by the key S-phase kinase complex, CDK2-cyclin A (38). The study by Pauls *et al* (47) suggested that the CDK6-dependent CDK2 phosphorylation of SAMHD1 inhibited its restriction activity against HIV-1 replication in primary cells. Therefore, the synergistic effect of CDK2 and CDK6 during cell cycle progression is essential for determining the susceptibility to HIV-1 infection by modulating viral dNTP access through SAMHD1. Notably, SAMHD1 is also phosphorylated at T592 from the G0 to G1 phase of the cell cycle through the activation of CDK2 and cyclin E expression, resulting in increased dNTP pools (47).

Furthermore, the levels of SAMHD1 phosphorylation at T592 may be reduced following treatment with type I IFN, reinforcing the link between the phosphorylation of SAMHD1

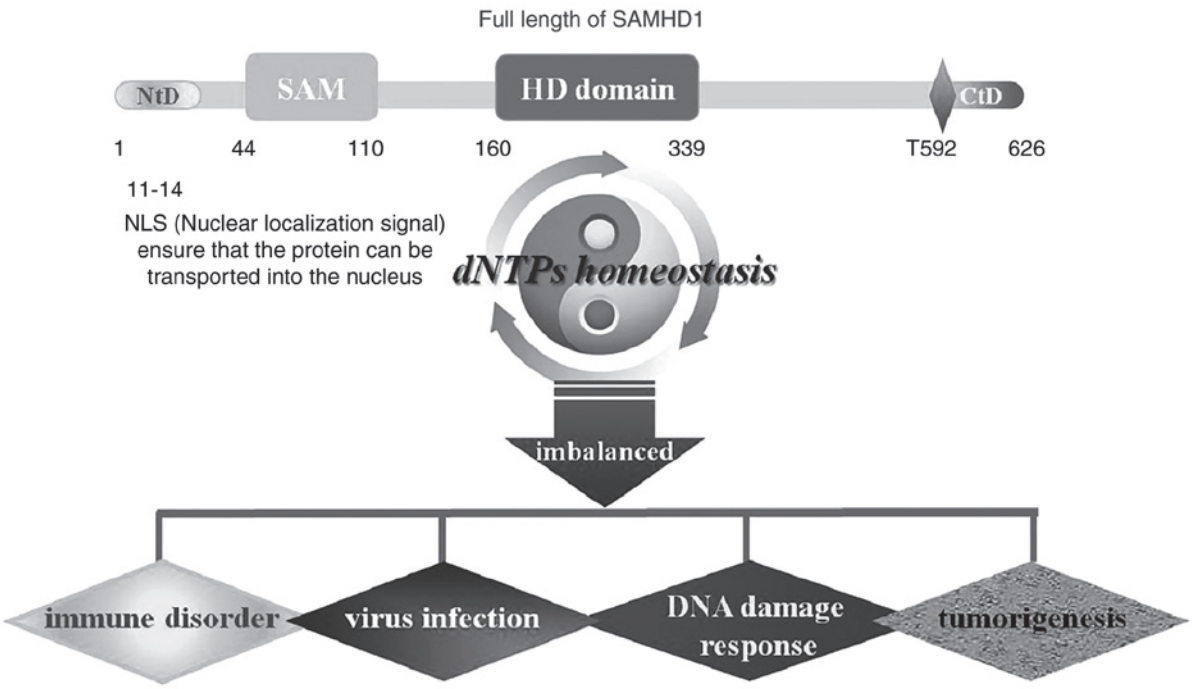

Figure 1. Overview of SAMHD1. SAMHD1, sterile alpha motif and histidine/aspartic acid domain-containing protein 1; dNTPs, deoxynucleotide triphosphates.

and its antiviral activity (46). Recently, several studies have suggested that the expression of $p21^{Waf1/Cip1}$ (referred to as p21), a CDK inhibitor, may lead to reduced phosphorylation at T592 residue by CDKs. Thus, SAMHD1 antiviral activity is regulated by CDK1 phosphorylation at amino acid T592, and type I IFN renders Vpx unable to induce SAMHD1 degradation (48-50). Type II IFN can stimulate the transcription of SAMHD1 to degrade dNTP and to restrict viral infection positively (51,52) and type III IFN exhibits modest to undetectable activity (53). However, further research is required in this field to explore the underlying molecular biological mechanisms.

The folding of the SAMHD1 region is disrupted around T592E due to negative charge repulsion generated by a phosphomimetic mutation. Subsequently, this disruption leads to the substantial destabilization of the active tetrameric form of SAMHD1 and an approximately 3-fold decrease in its dNTPase activity. However, the T592V variant does not perturb the crystal structure of SAMHD1; thus, the available active SAMHD1 tetramers are not significantly decreased (54). In addition, the importance of SAMHD1 dephosphorylation has also been investigated. Thus, phosphatase PP2A-B55α is responsible for rendering the antiviral activity of SAMHD1. These results suggest that phosphorylation and dephosphorylation at T592, the key regulatory site of SAMHD1 protein, is responsible for the diverse physiological functions of SAMHD1 (55).

Although alanine substitution at T592 exerts only a minimal effect on the viral restriction ability of SAMHD1 in differentiated U937 cells, phosphomimetic substitution by aspartate and glutamate completely eliminates its antiviral effect. In addition, introducing a T592A alanine mutation does not rescue SAMHD1 restriction in cycling U937 cells, suggesting that the inhibition of phosphorylation is not sufficient to restore SAMHD1 in proliferating cells (5,39). However, the antiviral activity of SAMHD1 is limited to non-cycling cells. As previously mentioned, SAMHD1 is phosphorylated on residue T592 in cycling cells; however, the phosphorylation dissipates when cells are in a non-cycling state, thus modulating the ability of SAMHD1 to block retroviral infection without affecting its dNTPase activity (6).

Moreover, it has been reported that SAMHD1 is acetylated on K405 by the acetyltransferase arrest defective protein 1 (ARD1) and enhances its dNTPase activity *in vitro*. However, the non-acetylated arginine substitution mutant (K405R) does not exert a similar effect. Compared with cells expressing wild-type SAMHD1, cancer cells expressing K405R mutant exhibit an attenuated G1/S cell cycle transition and a decreased cell proliferation. SAMHD1 acetylation levels are increased during the G1 phase of the cell cycle. Collectively, these findings suggest that SAMHD1 acetylation enhances its ability to hydrolyze dNTPs and promote cancer cell proliferation. Therefore, SAMHD1 may be a potent effective target for cancer treatment (3).

Finally, it has been documented that promoter hypermethylation suppresses the transcriptional regulation of *SAMHD1*, thereby downregulating its protein expression and its tumorigenesis-related functions (11-13).

SAMHD1 activity demonstrates a significant association between dNTP homeostasis and disease progression. Thus, further research on the post-translational modifications of SAMHD1 is urgently required in order for its additional benefits to be fully elucidated.

4. Role of SAMHD1 in dNTP homeostasis

SAMHD1, as a dNTP hydrolytic enzyme, plays a key role in the maintenance of homeostasis of cellular dNTP pools (20,56,57) and it is essential for preserving genome integrity. It has been

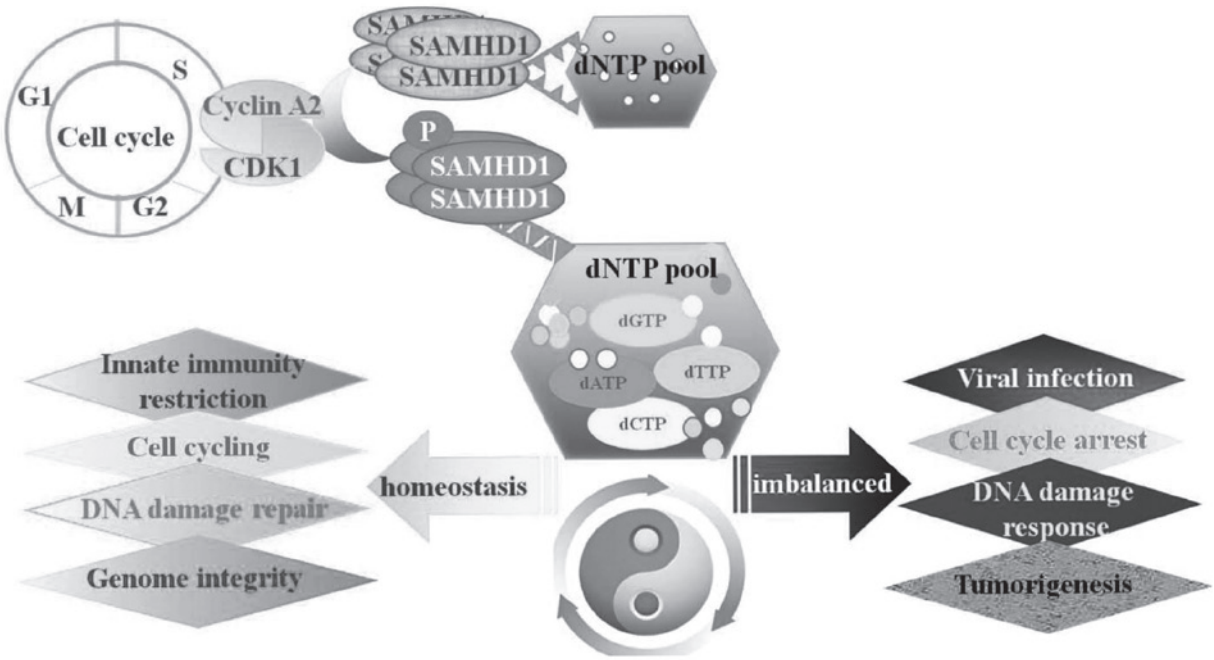

Figure 2. Role of SAMHD1. SAMHD1, sterile alpha motif and histidine/aspartic acid domain-containing protein 1; dNTP, deoxynucleotide triphosphate; CDK1, cyclin-dependent kinase 1.

reported that dNTP pool imbalance caused by SAMHD1 deficiency may lead to DNA damage, accompanied by the activation of IFN signaling (57). In addition, the surplus of dNTPs induces mismatches and increases the mutation rate during cellular DNA replication (58), which is an important molecular mechanism of tumorigenesis (1). There is increasing evidence to suggest that imbalanced dNTP levels are associated with the rate of replication fork formation under DNA replication stress, leading to gene mutations, genomic instability and cancer development (59,60). Therefore, SAMHD1 is considered a key regulator involved in the maintenance of the dNTP pool and genome homeostasis. The role of SAMHD1 is illustrated in Fig. 2.

5. Role of SAMHD1 in DNA damage response

DNA damage in cells, mainly single-strand breaks, arises frequently (approximately 10,000 lesions per cell per day) by a variety of endogenous and exogenous stimuli (61,62). It has been well established that the DNA damage response (DDR) pathway detects lesions in DNA strands and activates the repair system (63). Subsequently, cell cycle checkpoints are activated, providing sufficient time to allow lesions to be repaired. However, an unrepaired or improperly repaired DNA response leads to cell death or abnormal cell mitosis, which may induce malignant transformation and proliferation (64,65). Additionally, inherited defects in DNA damage repair mechanisms are associated with cancer predisposition (66), immunodeficiency (67), neurodegenerative disorders (68), infertility (69) and premature aging, highlighting the critical role of DDR in human health.

Several studies have demonstrated that SAMHD1 participates in the DDR process. Thus, SAMHD1 promotes dNTPase-independent DNA end resection to facilitate DNA double-strand breaks (DSBs) repair by homologous recombination (HR) (70). In addition, SAMHD1 exhibits a hydrolase-independent function though its C-terminal recruitment of interacting proteins (CTIP) to DSB sites. These observations suggest that SAMHD1 may contribute to anticancer therapy (71). Clifford *et al* (72) investigated the expression of SAMHD1 in patients with chronic lymphocytic leukemia (CLL) in the UK and revealed that SAMHD1 affected cell proliferation and survival following DNA damage induction. More specifically, the overexpression of wild-type SAMHD1 inhibited proliferation and increased cell death following DSB treatment. Furthermore, SAMHD1 was co-localized with p53-binding protein 1 (53BP1) at the DNA DSB site in the nucleus, which further indicated that SAMHD1 is involved in the DDR process and related diseases (72). By contrast, SAMHD1 downregulation may cause excess dNTPs and a subsequent imbalance of dNTP pools, resulting in base mismatches and mutations during replication, eventually leading to the activation of the intrinsic interferon signal (57). These findings indicate a novel association between SAMHD1 and DDR process in the pathogenesis of several diseases.

6. Role of SAMHD1 in immune disorders and viral infections

SAMHD1 is widely expressed in the majority of tissues and cells, and its restrictive function in the innate immunity has been extensively reviewed since it was first discovered. The *SAMHD1* gene mutation was detected in autoimmune AGS (22,73-75), which was first described by Jean Aicardi and Francoise Goutières in 1984 (76). The common clinical features of AGS overlap with the autoimmune disease systemic lupus erythematosus (SLE), including brain atrophy and severe sequelae (75,77,78). It has been reported that SAMHD1

mutations at residues 123, 143, 145, 201, 209, 254, 369 and 385 result in impaired endogenous SAMHD1 protein function and induce nucleotide metabolism disorders in myeloid cells (22). Abnormally increased dNTP pools in fibroblasts derived from patients with AGS are caused by the loss of functional SAMHD1. Subsequently, dNTP accumulation may induce the immune system to secrete excessive amount of antibodies, as it has been previously described (57). These results suggest that SAMHD1 is a key regulator of the immune system by maintaining nucleotide pool homeostasis.

Reverse transcription is a unique DNA synthesis process through which retroviruses and retrotransposons convert single stranded RNA genomes into double stranded DNA. This process is catalyzed by reverse transcriptase, which is a virally encoded DNA polymerase (79,80). Retroviruses consume cellular dNTPs regulated by SAMHD1 to convert their RNA genomes into proviral DNA through reverse transcription (81). DNTPs differ by only a single atom from ribonucleotide triphosphates (NTPs), yet are maintained at 10-1,000-fold lower concentrations (82). Ryoo *et al* also found that SAMHD1 restricted HIV-1 infection through its RNase activity by cleaving the viral RNA genome, and SAMHD1 associated with HIV-1 RNA and degraded it during the early phases of cell infection (31). The poor dNTP availability in macrophages infected with HIV infection mainly promotes viral mutagenesis induced by frequent rNMP and non-canonical dUMP incorporation (83,84). Finally, SAMHD1 may be a primitive cellular defense tool that was developed to effectively control the replication of dNTP-utilizing pathogens (81).

Human SAMHD1 is a key restriction factor against HIV-1 infection and is highly expressed in non-circulating cells, such as resting $CD4^+$ T cells and terminally differentiated macrophages. SAMHD1 limits HIV-1 infection in non-dividing cells by reducing the levels of intracellular dNTPs during viral reverse transcription, which is indispensable for viral storage and incubation (85). Thus, the overexpression of wild-type SAMHD1 inhibits HIV-1 long terminal repeat (LTR)-driven gene expression at the transcriptional level. In addition, it has been well documented that non-phosphorylated (T592A) and dNTPase inactive [H206D R207N (HD/RN)] mutants of SAMHD1 fail to efficiently inhibit HIV-1 LTR-driven gene expression or the latent virus reactivation (85). SAMHD1 has been reported to be a potent inhibitor of LINE-1 retrotransposition. SAMHD1 is a potent regulator of LINE-1 and LINE-1-mediated Alu/SVA reverse transcriptional transposon. It has also been found that the mutant of SAMHD1 has a defect in LINE-1 inhibition. At the same time, the ability of SAMHD1 to inhibit ORF2p-mediated LINE-1 RNP reverse transcription has been shown to be associated with SAMHD1-mediated LINE-1 inhibition (86). Furthermore, SAMHD1 attenuates IFN- and T-cell-mediated responses by suppressing the induction of virus-specific cytotoxic T-cells *in vivo* (87). Of note, HIV-2 and simian immunodeficiency viruses (SIVs) with Vpx or viral protein R (Vpr) can induce SAMHD1 degradation, by inhibiting SAMHD1 downregulation during viral infection (25,88-91). Additionally, it has been reported that SAMHD1 blocks feline immunodeficiency virus (FIV), bovine immunodeficiency virus (BIV), equine infectious anemia virus (EIAV), N-tropic murine leukemia virus (N-MLV) and B-tropic murine leukemia virus (B-MLV) infections (92). These findings indicate that SAMHD1 exerts inhibitory effects on infectious diseases.

7. Role of SAMHD1 in tumorigenesis and cancer treatment

Recently, SAMHD1 has been shown to be associated with the development of CLL (72,93). Thus, *SAMHD1* gene mutations have been detected in leukemia cells, and SAMHD1 mRNA and protein expression levels have been found to be significantly and differentially downregulated. The loss-of-function mutation of *SAMHD1* usually occurs early in the evolutionary stage of the molecular cloning of CLL and promotes the development of the disease. In addition, some *SAMHD1* mutations are detected in both AGS and CLL, thus AGS patients with *SAMHD1* mutations are more likely to suffer concomitant CLL (72).

Several studies have demonstrated that SAMHD1 is associated with the development of multiple types of cancer, such as lung and colon cancer. Thus, in lung adenocarcinoma, SAMHD1 mRNA and protein levels have been shown to be downregulated compared with those noted in adjacent normal tissues. In addition, it has been suggested that the *SAMHD1* promoter is highly methylated in lung adenocarcinoma, resulting in a suppressed SAMHD1 expression (13). Similarly, frequent mutations in *SAMHD1* in colon cancer cells induce SAMHD1 downregulation (94). The aforementioned results suggest that SAMHD1 is closely associated with an increased risk of both lung and colon cancer, and presumably with other types of cancer.

Recently, it was demonstrated that a low level of exogenous SAMHD1 expression can significantly reduce the growth, proliferation and colony formation of HuT78 cells by increasing apoptosis; thus, it may play a potential anticancer role in cutaneous T cell lymphoma (CTCL) (95). In view of the role of SAMHD1 in maintaining genomic stability, it may play an additional role in cells as a cancer suppressor enzyme.

Exogenous SAMHD1 expression in HuT78 cells has also been shown to result in increased spontaneous and Fas ligand (Fas-L)-induced apoptosis levels via the activation of the extrinsic pathway, including caspase-8, -3 and -7. Mechanistically, SAMHD1 expression in HuT78 cells leads to a significant reduction in the expression of cFLIPS, a key anti-apoptotic regulator that is commonly overexpressed in patients with CTCL (95-97).

The catalogue of somatic mutations in cancer (COSMOS) records 164 unique mutations in SAMHD1 found in samples from various cancer tissues (98). Widely expressed in several tissues, *SAMHD1* mutations have also been detected in breast cancer, myeloma, pancreatic cancer and others. The mutation and modification sites of SAMHD1 in different types of cancer are presented in Tables I (99-104) and II, respectively.

The importance of SAMHD1 in dNTP metabolism and genome integrity has been well established; thus, strategies targeting *SAMHD1* gene replication, post-translational modifications and protein expression have been evaluated for the treatment of cancer and autoimmune diseases (105). SAMHD1 acetylation enhances its dNTPase activity, and thereby, cancer cell arrest at the G1 phase to aid G1/S phase transition and promote cell cycle progression. This observation suggests that the acetylation level of SAMHD1 may be a potential

Table I. Modifications to SAMHD1 in various human diseases.

Type of disease	Modifications	Modifications to SAMHD1	
		Results	(Refs.)
Breast cancer	N.A.	Reduction in protein	(99)
Skin T-cell lymphoma	Methylation	Reduction in protein and mRNA	(95,100)
Lung cancer	Methylation	Reduction in protein and mRNA	(101,102)
Colorectal cancer	N.A.	N.A.	(94,99,103)
Cervical cancer	Acetylation	N.A.	(3)
HIV-1	Phosphorylation	Reduction in protein	(19,53)
AGS	N.A.	Reduction in protein	(104)
HBV	Phosphorylation	N.A.	(43,44)
HSV-1	Phosphorylation	N.A.	(41,42)
EBV	Phosphorylation	N.A.	(9)
HCMV	Phosphorylation	N.A.	(10)

N.A., no information available; SAMHD1, sterile alpha motif and histidine/aspartic acid domain-containing protein 1; HIV-1, human immunodeficiency virus 1; AGS, Aicardi-Goutières syndrome; HBV, hepatitis B virus; HSV-1, herpes simplex virus 1; EBV, Epstein-Barr virus; HCMV, human cytomegalovirus.

Table II. Mutations of *SAMHD1* in different human cancers.

Type of cancers	Frequency (%)	Mutation type	Mutations of *SAMHD1*		
			DNA alterations	Results	(Refs.)
Skin cancer	53.01	Multipoint	chr20:g.35551400G>A	N.A.	N.A.
Liver cancer	24.42	Multipoint	chr20:g.35585008A>-	Reduction in protein	(43)
Blood cancer	14.29	Single point	chr20:g.35559188C>A	N.A.	N.A.
Breast cancer	12.13	Multipoint	chr20:g.35513711A>-	Reduction in protein	(99)
Lung cancer	11.76	Multipoint	chr20:g.35518800T>C	Reduction in protein and mRNA	(13)
Pancreatic cancer	7.84	Multipoint	chr20:g.35519255C>T	N.A.	N.A.
Prostate cancer	1.54	Single point	chr20:g.35517455T>A	N.A.	N.A.
Cervical cancer	0.52	Single point	chr20:g.35515883C>G	N.A.	N.A.

N.A., no information available; SAMHD1, sterile alpha motif and histidine/aspartic acid domain-containing protein 1.

therapeutic target for cancer treatment. In addition, this finding also unveils a potential method for therapeutically targeting SAMHD1 activity in cells through the use of small molecule inhibitors of acetyltransferases (3). Furthermore, SAMHD1 protects cancer cells from several antinucleoside metabolite treatments, such as cytarabine (Ara-C) which is mainly used in the treatment of acute myeloid leukemia (AML) (106-109). Combination therapy with an anthracycline (commonly doxorubicin or daunorubicin) and Ara-C is the standard treatment for AML (110). Ara-C is converted by the canonical dNTP synthesis pathway to Ara-CTP, the active triphosphate of Ara-C, which serves as a substrate of SAMHD1 (107). Herold *et al* (106) demonstrated that wild-type SAMHD1 reduced Ara-C treatment efficacy *in vivo* in an AML mouse model. In addition, THP-1 cells lacking a functional *SAMHD1* gene have been shown to exhibit an increased sensitivity to antimetabolites, including fludarabine, decitabine, vidarabine and clofarabine (106). SAMHD1 downregulation or the inhibition of its post-translational modifications may be promising strategies with which overcome tumor resistance. Therefore, SAMHD1 is considered a potential biomarker for the stratification of patients with AML and a target for the treatment of Ara-C-refractory AML (109). The aforementioned findings suggest that the invention of a potent SAMHD1 inhibitor that enhances the efficiency of nucleotide analogues should perhaps be a top priority for researchers. Thus, high-throughput assays have already been established from several research groups (111,112). Such approaches seem to be particularly promising for future developments in this field.

8. Conclusions and future perspectives

Studies on the unique, natural viral restriction and dNTPase properties of SAMHD1 have demonstrated its involvement in

the pathogenesis of several diseases and have provided guidance for progress in the development of clinical applications. More specifically, studies on the underlying mechanisms of antiviral agents to fight infection have revealed that SAMHD1 inhibits HIV-1 infection in non-dividing cells by restricting viral reverse transcription, resulting in decreased virus activity and storage (14,15,113,114). In addition, SAMHD1 inhibits SIV activity containing Vpx or Vpr (116-118).

The dNTPase activity of SAMHD1 maintains balanced cellular dNTP pools, thus preventing genomic instability and tumorigenesis. *SAMHD1* loss-of-function mutations are associated with abnormal dNTP accumulation, which induces rapid cancer cell proliferation (37,105,119,120) and immune system disfunctions. On the other hand, SAMHD1 protects cancer cells from DNA replication inhibitors, such as pyrimidine antimetabolite antitumor agents (104,105).

Therefore, future studies on SAMHD1 may provide further insight into the clinical treatment of cancer and other severe diseases. Finally, strategies targeting SAMHD1 are expected to provide more effective health-related interventions.

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Availability of data and materials

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Authors' contributions

XS and LC designed and conceived the general idea and context of this review article. XS, LC and ZZ conceived and wrote the Abstract. ZZ and YY conceived and wrote the Introduction and 'Overview of SAMHD1' sections. LZ and JW contributed to the 'Modifications of SAMHD1' and the 'Role of SAMHD1 in dNTP homeostasis' sections. FY, YX and QG conducted the writing of the 'Role of SAMHD1 in DNA damage response' and 'Role of SAMHD1 in immune disorders and viral infections' sections. XW and SC completed the 'Role of SAMHD1 in tumorigenesis and cancer treatment' sections. ZZ integrated all sections and relevant references of this manuscript. XS, LC and ZZ revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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