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SAMHD1: Recurring roles in cell cycle, viral restriction, cancer, and innate immunity

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Abstract

SAMHD1 is a deoxynucleotide triphosphate (dNTP) hydrolase that plays an important role in the homeostatic balance of cellular dNTPs. Its emerging role as an effector of innate immunity is affirmed by mutations in the SAMHD1 gene that cause the severe autoimmune disease, Aicardi-Goutieres syndrome (AGS) and that are linked to cancer. Additionally, SAMHD1 functions as a restriction factor for retroviruses such as HIV. Here we review the current biochemical and biological properties of the enzyme including its structure, activity, and regulation by post-translational modifications in the context of its cellular function. We outline open questions regarding the biology of SAMHD1 whose answers will be important for understanding its function as a regulator of cell cycle progression, genomic integrity, and in autoimmunity.

Keywords

SAMHD1; dNTP metabolism; nucleotide; autoimmune disease; Aicardi-Goutieres syndrome; HIV

Deoxynucleotide Metabolism Overview

Proper regulation of intracellular deoxynucleotide triphosphates (dNTPs) is essential for normal cellular metabolism. dNTPs differ by only a single atom from ribonucleotide triphosphates (NTPs) yet are maintained at 10–1000 times lower concentration (1). A balanced supply of each of the four canonical dNTPs maintained at proper concentrations is required for accurate genomic and mitochondrial DNA synthesis and repair (2–5). As such, nucleotide metabolism is precisely regulated within cells. Organisms have evolved complex and dynamic mechanisms and checkpoints to control the synthesis and degradation of dNTPs (Fig. 1) (6, 7). The enzymes involved in these pathways are frequently regulated in a concentration dependent manner by their respective substrates and products (8–12). Synthesis of dNTPs is accomplished by way of two distinct pathways; the *de novo* synthesis

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and the salvage pathways (2, 4). During *de novo* synthesis, cytosolic ribonucleotide diphosphates are reduced to deoxynucleotide diphosphates (dNDPs) by the enzyme ribonucleotide reductase (RNR) (13). dNDPs are then phosphorylated by cytosolic or mitochondrial kinases. This process is dramatically upregulated during S-phase, when the cell requires large amounts of dNTPs to replicate its DNA, and intracellular dNTPs concentrations increase 5–10 fold over early G_1 levels (2, 6, 7). *De novo* synthesis of nucleotide triphosphates is also important for supplementing intracellular nucleotide pools required for genome maintenance during other stages of the cell cycle and is carried out by a second isoform of RNR regulatory subunit at a reduced rate (14–17). The salvage pathway is constitutively active and performed in parallel in both the cytosol and mitochondrial compartments. It is essential for maintaining dNTP pool levels for nuclear and mitochondrial DNA synthesis and repair in resting cells by recycling cellular deoxynucleosides that are products of nucleic acid degradation, cellular nucleotidases, or imported from the extracellular space (6).

Opposing the *de novo* and salvage anabolic pathways, various enzymes function together to comprise the catabolic pathways that facilitate the degradation of dNTPs. 5’-nucleotidases, nucleoside phosphorylases, and deaminases are responsible for breaking down dNTPs into the constituent deoxynucleoside or nucleobase, at which point they can reenter the salvage pathway or be transported across the cell membrane in order to maintain the overall size and ratio of intracellular dNTPs(18). The opposing anabolic and catabolic pathways work in competing directions to maintain a dynamic equilibrium of intracellular dNTPs in a process referred to as substrate cycling (19). Isotope flow experiments of radiolabeled nucleotides have traced this phenomenon and elucidated its critical role as a regulatory mechanism for maintaining homeostatic dNTP levels (20–22). It is also important to note that cytosolic dNTP pools do not exist in isolation, but are directly related to mitochondrial dNTP pools. In fact, dNTP precursors transport between the two compartments and the nucleotide metabolism processes of one compartment can influence the other (23, 24).

Substrate cycling, DNA synthesis and repair, and nucleoside import and export form a dynamic regulatory system that maintains homeostatic dNTP concentrations within the cell. The levels are finely tuned according to the cell type and stage in the cell cycle. Each canonical dNTP is not equally abundant within the cell, however. dGTP is consistently observed to be least prevalent in eukaryotic cells (2, 4). While dNTP concentrations are asymmetric, the proper balance of the dNTP pool is crucial to cell survival and genomic integrity(25). Imbalanced dNTP pools, resulting from DNA damage, metabolic dysregulation, or mutations to the enzymes involved in maintaining dNTP equilibrium, can result in harmful consequences including: increased mutation rates and the induction of a mutator phenotype; increased DNA damage and activation of the DNA damage response; altered DNA polymerase kinetics, replication stress, and collapsed or stalled replication forks; altered replication origin spacing and usage; modified epigenetic profiles and gene expression; and restricted cell cycle progression (26–39). These molecular perturbations of genomic fidelity manifest themselves as severe pathologies including mitochondrial depletion syndromes, severe immunodeficiency disorders, induced cellular senescence, and cancer (40–47). Imbalanced dNTP pools may also impact apoptosis and inflammation, as dNTPs have been implicated in the activation of both pathways (47–50).

SAMHD1 Activation, Catalysis, and Regulation

SAMHD1 Activation and Catalysis.

Sterile Alpha Motif and Histidine-Aspartic acid domain containing protein 1 (SAMHD1) is a deoxynucleotide triphosphate (dNTP) hydrolase that catalyzes the hydrolysis of canonical dNTPs into the constituent nucleoside and inorganic tripolyphosphate. Through its dNTPase activity, SAMHD1 maintains dNTP pools within the cell at levels appropriate for DNA replication and repair but below a potentially mutagenic threshold. SAMHD1 was first discovered in 2000 as an ortholog of the mouse interferon-γ induced dendritic cell protein MG11 but the precise function of the enzyme remained unclear (51). It was not until almost 10 years after its initial discovery that SAMHD1 was implicated in nucleotide metabolism and demonstrated to exert a potent immunomodulatory effect (52). Subsequent biochemical analysis revealed the hydrolase catalytic activity of the enzyme, divalent metal ion dependence, and activation by guanosine nucleotides (53–57) (Fig. 2). Additionally, structural and functional similarities of SAMHD1 with several prokaryotic homologues have been observed (58–64). These bacterial enzymes provided an initial template for interrogating the cellular role of SAMHD1, as well as the structural mechanisms of activation and catalysis.

SAMHD1 is a 626 amino acid protein comprised of an N-terminal sterile alpha motif (SAM) and a histidine-aspartic acid containing domain (HD). While the role of the SAM domain remains an open question, SAM domains are commonly involved in protein-protein and protein-DNA/RNA interactions (65). A nuclear localization signal precedes the SAM domain and confers the nuclear occupancy observed in most studies (66, 67). The HD domain is defined by its characteristic quartet of metal coordinating histidine and aspartic acid residues within the enzyme active site. HD-domain containing proteins represent a superfamily of phosphohydrolases commonly involved in nucleic acid metabolism (68). The HD domain of SAMHD1 houses the dNTPase active site, regulatory sites, and the requisite interfaces for enzyme oligomerization. The C-terminus of SAMHD1 consists of a distinct region that is important for stabilizing the oligomeric state of the enzyme and nucleic acid interaction (69–71). X-ray crystallographic studies have illuminated the structural features and catalytic mechanism of SAMHD1 (Fig. 3). The apo-SAMHD1 protein exists in a monomer-dimer equilibrium, but tetramerizes in the presence of activating nucleotides in order to form the catalytically competent holoenzyme (57, 71, 72). Each SAMHD1 monomer contains two discrete regulatory sites (RS1 and RS2) and activating nucleotide triphosphates must sequentially bind at each site in order to induce a conformational shift that facilitates tetramerization and subsequent catalytic activation (57, 70, 71). The residues which constitute the RS1 pocket are uniquely structured such that only a guanosine triphosphate nucleotide is capable of binding with an estimated K_d between 0.1–0.4 μM (53, 55, 57, 73, 74). Given the 1000-fold excess of GTP over dGTP within cells, it is likely that RS1 is constitutively occupied by GTP as a primary activating nucleotide under physiological conditions (55, 56, 73). GTP binding at RS1 drives the oligomeric equilibrium toward the dimer as the GTP nucleotide forms contacts with both subunits. Further studies have suggested that constitutive binding of GTP by SAMHD1 can form relaxed tetramers

that are primed for full assembly and high-efficiency catalysis upon binding of a second activating nucleotide at RS2 (75).

In contrast to RS1, RS2 presents a more promiscuous binding site. RS2 can accommodate any of the four canonical dNTPs with apparent K_d values between 1–20 μM depending on the nucleobase (57, 73, 76–78). These concentrations are physiologically relevant and thus binding of a dNTP in the RS2 of SAMHD1 occurs when intracellular dNTP concentrations are elevated into the activating range (24). While RS2 is capable of binding any of the four dNTPs, there is a clear preference for purine nucleotides (57, 76). Thus, given the asymmetric nature of dNTP pools within the cell, it is likely that dATP is most frequently docked in RS2 (73). While dATP may be the primary nucleotide bound in RS2, it is possible that the specific dNTP docked in RS2 may confer differential stability and substrate specificity to the activated enzyme (77).

The binding event of a dNTP at RS2, which is preceded by docking of GTP in the guanine specific RS1 pocket, stabilizes a dimer of dimers and drives the oligomeric equilibrium towards tetramerization. Subunit assembly results in the formation of four regulatory clefts comprised of an RS1 and RS2 from adjacent monomers, as well as the residues of a third SAMHD1 subunit. The two nucleotides bound in each cleft are coordinated by a single divalent cation (commonly Mg^{2+}) that stabilizes their phosphate tails. At each of the four occupied regulatory sites in the activated tetramer, the activating nucleotides form a network of hydrogen bonds, electrostatic, and pi-pi orbital interactions with residues from the three distinct monomers that comprise the cleft. This results in a thermodynamically stable SAMHD1 tetramer housing eight total activating nucleotides (4xd/GTP and 4xdNTP) bound in the four regulatory clefts. Tetramer assembly is further enhanced by several key structural motifs, specifically protein-protein interfaces formed by an ordering of the C-terminus (amino acids 454–599), and a long alpha helix (amino acids 352–373) that significantly contributes to the dimer-dimer interface (57, 70, 71, 74). Binding of activating nucleotides and the subsequent formation of the tetramer result in conformational changes that remodel the active site allowing substrate binding and catalysis.

It has been suggested that the catalytically active tetrameric species can persist for extended periods even after dNTP levels have diminished below the effective level for SAMHD1 activation (55, 77). This long-lived active state may be important for maintaining cellular dNTP pools at the extremely low concentrations observed in non-cycling cells. Regardless of the duration of the activity, the elegant and strictly regulated mechanism of SAMHD1 catalytic activation represents an ordered and sequential process in which dNTPs serve as both substrate and activating ligand. The finely-tuned autoregulatory mechanism enables SAMHD1 to sense small fluctuations of dNTP concentrations within the cell and respond accordingly by degrading them to physiologically appropriate levels.

Nucleobases are stabilized in the active site through a series of non-specific interactions with water molecules, which likely affords SAMHD1 substrate promiscuity (57, 70, 71, 74). In addition to the ability to hydrolyze all four canonical dNTPs and dUTP, the SAMHD1 active site is also able to accommodate base modified substrates (79). Hydrolysis of base-modified or non-canonical nucleotides may represent additional cellular functions of SAMHD1,

although this aspect of its activity has not been rigorously interrogated. dNTPs are oriented for chemistry to occur through an interaction between their α-phosphate and a Mg^{2+} ion coordinated by the His167-His206-Asp207-Asp311 quartet characteristic of HD domains. His210, His233, and Asp218 are believed to be the residues responsible for actual catalysis, which occurs through an in-line nucleophilic attack at the α-phosphate resulting in tripolyphosphate and the cognate nucleoside as reaction products (80). Steric clashes with active site residues by the 2'-hydroxyl group found on ribonucleotides preclude efficient rNTP binding and hydrolysis.

Despite the substrates of SAMHD1 also serving as its activators, SAMHD1 displays little evidence of cooperative kinetics. The sequential activation and assembly of the SAMHD1 tetramer occur at dNTP concentrations multiple orders of magnitude below the K_M. Thus, while reported K_M values for SAMHD1 vary considerably from 50–350 μM depending on the study, standard Michaelis-Menten kinetic models apply under all the experimental conditions measured (55, 57, 73, 78, 81, 82). Given the steady-state conditions of an activated SAMHD1 tetramer, the turnover rate for each substrate appears to depend solely on its particular affinity for the active site and its intracellular concentration. Recent evidence however, is interjecting questions into this model. In a manner resembling ribonucleotide reductase activation, the particular dNTP bound in the RS2 may influence substrate specificity and catalytic efficiency (78). The precise nature of SAMHD1 activation and substrate specificity *in vivo* is an open inquiry that requires further investigation into the underlying molecular mechanism and physiological significance.

SAMHD1 Nucleic Acid Interaction.

In addition to its dNTPase activity, SAMHD1 is also a nucleic acid binding protein. SAMHD1 binds DNA and DNA:RNA duplexes, but preferentially binds single stranded nucleic acid polymers (ssNAs), with a greater affinity for ssRNA over ssDNA (83–85). The specific affinity of SAMHD1 for ssNAs may be regulated by their secondary structure (86). The phenomena of SAMHD1 ssNA interaction has also been reported in cells where multiple SAMHD1 monomers converge on sites of ssRNA or ssDNA (87). It also appears that monomeric SAMHD1 primarily interacts with nucleic acids, and that SAMHD1 monomers can form multi-subunit complexes in the presence of ssNA that are distinct from the oligomeric forms induced by dNTPs (83).

Efficient interaction with ssNAs involve residues from both the HD domain and C-terminus, with the C-terminus peptide (residues 583–626) demonstrating nucleic acid binding even in the absence of the HD and SAM domains (83, 88). Interestingly, nucleic acid binding by SAMHD1 inhibits dNTPase activity by obstructing the interfaces responsible for tetramer association. This obstruction can be relieved by increasing the concentration of activating nucleotides (88). SAMHD1 has also been reported to exhibit exonuclease activity on ssRNA and ssDNA (86, 89, 90). The proposed mechanism of catalysis for SAMHD1 exonuclease activity is a phosphorolytic cleavage of the phosphodiester bond in nucleic acid polymers (91). These findings are widely contested however, as many groups report not being able to detect SAMHD1 nuclease activity or its effect on viral restriction (53, 83, 84, 92, 93). Instead, they propose that co-purification of a contaminating nuclease is responsible for the

observed exonuclease activity of SAMHD1. While the precise function of nucleic acid interaction in cells is yet to be determined, a recent report suggests that the ability of SAMHD1 to interact with DNA may play a crucial role in facilitating the repair of DNA. In this study, SAMHD1 was demonstrated to localize to sites of double stranded breaks and promote homologous recombination through its ability to form a complex with the endonuclease CtBP interacting protein (CtIP) (94). This description of a previously unidentified SAMHD1 role in DNA damage repair broadens the scope of the enzyme's cellular functionality, and underscores the importance of further investigation of the dynamic cycle between nucleic acid bound inactive monomer-dimer and catalytically active tetramer.

SAMHD1, Cellular Regulation, and Nucleotide Metabolism

SAMHD1 expression profile and regulation.

SAMHD1 was initially termed dendritic cell derived IFN-γ induced protein (DCIP) following its identification in dendritic cells as the human ortholog of an interferon-γ induced mouse protein (51). While the precise function of DCIP (SAMHD1) remained unknown, it was subsequently determined to be upregulated in lung fibroblasts in response to TNF-α or LPS induced acute injury in an IRF-1 dependent manner (95). Further studies eventually elucidated the integral function the enzyme performs in nucleotide metabolism and innate immunity within the cell, and in keeping with this critical role, SAMHD1 was revealed to be widely expressed in most human cells (96).

Although SAMHD1 is detected in almost all tissues, its expression levels vary by cell type and cell cycle phase. Quiescent primary human fibroblasts demonstrated a dramatic increase in SAMHD1 protein levels over proliferating fibroblasts, and this increase in SAMHD1 coincided with a decrease in intracellular dNTP pools (97). In contrast to fibroblasts, SAMHD1 is constitutively expressed at high levels in both cycling and non-cycling myeloid and lymphoid cells, including monocytes, macrophages, dendritic cells, and CD4+ T-cells, although its activity can be differentially regulated by post-translational modification (96, 98, 99). There is also experimental evidence to suggest that terminal differentiation of monocytes into macrophages or dendritic cells can further increase the expression levels of SAMHD1 (100). In hematopoietic cells where SAMHD1 is expressed and active, it contributes to the maintenance of dNTP levels that range from 3–250 fold lower than in those cells where it is post-translationally down-regulated, such as in activated human CD4+ T cells (101–103).

Given the cyclic and dynamic nature of nucleotide metabolism, the catalytic activity of SAMHD1 as a modulator of nucleotide pools is tightly controlled. Regulation of SAMHD1 begins at the transcriptional level, as several studies have demonstrated that the SAMHD1 promoter can be silenced by methylation (104–106). Two naturally occurring splice variants of SAMDH1 have been identified, consisting of truncated versions of the full-length protein (107). The utility of these isoforms is a subject of uncertainty however, as both were demonstrated to be metabolically unstable, catalytically inactive, and rapidly degraded in cells. In this way, human SAMHD1 diverges from its closely studied murine homologue, as mice express two catalytically competent SAMHD1 isoforms (108).

In keeping with its discovery as an interferon associated protein, SAMHD1 can be transcriptionally upregulated in some cell lines in response to cytokine (Il-12 and Il-18) or type-1 interferon (IFN1) treatment (102, 109, 110). Not all cells however, including macrophages, dendritic cells, and CD4+ T-Cells, exhibit an increase in SAMHD1 protein expression following exposure to IFN1 (96, 102, 109, 111). This discrepancy may be in part explained by the already elevated levels of SAMHD1 or by the inability of specific cell types to respond to IFN1 exposure by downregulating microRNAs that post-transcriptionally repress SAMHD1 translation (112). SAMHD1 expression can also be induced by viral challenge in an IRF3 dependent manner. Phosphorylated IRF3, a downstream transcription factor activated by intracellular pathogen pattern recognition receptors that coordinates the early immune response, was demonstrated to directly bind the SAMHD1 promoter and enhance SAMHD1 expression, thus corroborating the important role SAMHD1 plays as an effector of innate immunity (110).

Following translation of SAMHD1, little is known about its cellular half-life or subcellular interactions. Several studies however, have exposed protein interaction partners that provide clues as to the mechanism of normal SAMHD1 degradation. SAMHD1 interaction with both cyclin L2 and eukaryotic elongation faction 1A1 (eEF1A1) facilitates recruitment to the ubiquitin ligase machinery and subsequent proteosomal degradation (113, 114). A more recent study suggests that interaction with the transmembrane tetraspanin CD81 promotes proteosomal turnover of SAMHD1 (115). Interestingly, in the absence of CD81, SAMHD1 subcellular localization partially overlapped with EEA1, a marker of early endosomes. These findings reveal the initial associations and pathways in what is likely a complex network of interactions and regulatory layers that govern SAMHD1 expression and cellular half-life. Future research to clarify the precise relationships of this network will be important for understanding SAMHD1 functionality within the larger processes of nucleotide metabolism and innate immunity.

SAMHD1 regulation by post-translational modification.

While biochemical and structural studies have rigorously characterized the mechanism of SAMHD1 activation and catalysis, an emerging area of interest is the effect of post-translational modifications on SAMHD1 activity. Both human and murine SAMHD1 are phosphorylated at multiple sites (108, 116), but the most extensively studied is phosphorylation at its C-terminal T592 residue (P-T592) (98, 117). Phosphorylation of SAMHD1 at T592 occurs in a cell cycle dependent fashion by cyclin-dependent kinases 1 and 2 (CDKs) and coincides with an increase in intracellular dNTPs prior to S-phase DNA replication (93, 98–100, 118–121). Phosphorylation of the enzyme is mediated by the presence of a putative cyclin-binding motif located in the HD domain (residues 450–455), as well as a bipartite cyclinA2-CDK complex binding motif located in the C-terminus (99, 118). Further investigation of this regulatory axis reveals that SAMHD1 phosphorylation likely occurs as cells emerge from a G_0/quiescent state and transition through G_1 facilitated by a mitogen induced activation of the Raf/MEK/Erk kinase cascade (122). Conversely, for cells residing in a non-cycling G_0/quiescent state, multiple studies report that the dephosphorylated SAMHD1 species predominates and corresponds with reduced dNTP levels (98, 99, 117).

In addition to cell cycle phase, other cellular processes modify the phosphorylation status of SAMHD1 at T592. In CD4+ lymphocytes, cytokine (IL-7 or IL-2) activation or PHA treatment, was demonstrated to increase phosphorylation of SAMHD1 at T592 (96, 119, 120). Alternatively, IFN1 treatment results in the dephosphorylation of SAMHD1 at T592 (98). IFN1 signaling impedes cell cycle progression by up-regulating the cell cycle inhibitor $p21^{cip1/waf1}$ which subsequently restricts the activity of CDKs (123). Accordingly, monocyte derived dendritic cells (MDDC) matured in the presence of IFN-γ and CD40L, or M-CSF, demonstrated a decrease in phosphorylated SAMHD1 that corresponded to an increase in $p21^{cip1/waf}$ and a decrease in cellular dNTP pools (124, 125). DNA damage can also activate p21 and result in the concomitant loss of phosphorylated SAMHD1 in a p53 dependent manner, as described in a recent study in which macrophages were treated with topoisomerase inhibitors in order to induce a DNA damage response (126).

Given that phosphorylation of SAMHD1 occurs prior to S-phase and coincides with increased dNTP levels within cell, many have speculated that this modification is a requisite condition for altering the dNTPase capacity of the enzyme to promote DNA replication. The precise effects of phosphorylation on SAMHD1 activity are still under debate, however. Some evidence suggests phosphorylation negatively modulates SAMHD1 tetramerization and dNTPase activity (81, 99, 127), and this diminished dNTPase capacity is responsible for increased intracellular dNTP pools (93, 120, 121, 128). Other studies find limited or no effect of phosphorylation of SAMHD1 on catalytic activity(81, 108, 116, 117, 129), oligomerization equilibrium and allosteric activation(77, 129), or nucleic acid binding (83). Complicating the model further, phosphorylation may affect SAMHD1 substrate specificity (78).

Studies attempting to shed light on these discrepancies reveal that P-T592 results in altered kinetics of tetramer association and dissociation and expedited regulatory nucleotide release (77, 129). P-T592 is also less likely to form the activated tetramer at low concentration of activating nucleotides (78, 81). Structural data support these findings by identifying protein conformational shifts induced by a phosphomimetic mutant (T592E) that destabilizes the tetramer interface (127). Taken in sum, these data appear to indicate that phosphorylation at T592 is a mechanism for calibrating SAMHD1 activity through altering the thermodynamics of subunit association. The discrepant results may stem from variations in culture conditions or assay methods that lack the sensitivity to accurately capture the true effect of phosphorylation. Fine tuning SAMHD1 activity within the cell by phosphorylation, as opposed to a binary on or off state, may be important as a complementary method of regulation in order to maintain dNTP pools within the narrow window conducive to genomic integrity.

Two additional post-translational modifications have been discovered that regulate SAMHD1 catalytic activity. A recent study demonstrated that SAMHD1 catalytic activity is regulated by redox signaling (82). Redox signaling takes the form of reactive oxygen species (ROS) that are generated by cellular oxidases in response to growth factors binding and activating cellular receptors (130). These ROS act as secondary messengers that can covalently, but reversibly, interact with an enzyme to modify its tertiary structure and subsequent activity(131). SAMHD1 is catalytically inactivated when treated with the

oxidizing agent H_2O_2 in a dose dependent but reversible manner (82). Oxidation of SAMHD1 was demonstrated to inhibit tetramerization, but this deficiency was ablated in SAMHD1 mutants containing a C522A mutation. Closer inspection of SAMDH1 crystal structures reveal that C522 comprises one member of a cysteine triad - C522, C341, and C350 - that resides adjacent to the regulatory nucleotide binding site RS2. In several available crystal structures (pdbid: 5AO4, 4RXO, 4MZ7, 3U1N)(54, 70, 74, 81), a disulfide bond exists between C341 and C350 and results in a conformational shift that may disrupt activating nucleotide binding and tetramer stability. While the experiments in the study were performed using recombinant human SAMHD1, it is interesting to note that the residues comprising the cysteine triad (C522, C341, and C350) are highly conserved among vertebrate SAMHD1 homologues. The conserved nature of these residues in varying species underscores the likely importance of redox signaling as a central regulatory mechanism for modulating SAMHD1 activity *in vivo*.

The redox sensitivity of SAMHD1 was recapitulated in cells during experiments in which SAMHD1 was demonstrated to be oxidized in response to proliferative signals (82). It was proposed that cells oxidize SAMHD1 in response to proliferative signaling in order to accumulate the dNTPs necessary for DNA replication. This oxidation effect is mediated by the cysteine triad, referred to as a ‘redox switch’, which can detect ROS secondary messengers and translate them into structural rearrangements that alter SAMHD1 catalytic activity. Importantly, this phenomenon is reversible and tightly controlled.

SAMHD1 was also revealed to be acetylated both *in vitro* and in cells on the K405 residue by the acetyltransferase Arrest Defective Protein 1 (ARD1) (132). Like the conserved cysteine residues of the redox switch, K405 is conserved in many vertebrate SAMHD1 homologues indicating acetylation at this residue may play an important role in regulating SAMHD1 activity. Acetylation of SAMHD1 peaked during the G_1 phase of the cell cycle and resulted in the increased dNTPase activity of the enzyme *in vitro*. It was suggested, somewhat counter intuitively, that the enhanced dNTPase activity aided in G_1 to S-phase transition and promoted cell cycle progression in cancer cells. In addition to identifying a novel posttranslational modification, this finding also unveils a potential method for therapeutically targeting SAMHD1 activity in cells through the use of small molecule inhibitors of acetyltransferases.

As with phosphorylation, redox regulation and acetylation of SAMHD1 represent means of control orthogonal to catalytic activation and protein expression that can be localized spatially and temporally. These post-translational modifications work as additional levers of SAMHD1 control to precisely calibrate SAMHD1 activity. The meticulously controlled dynamic gradient of SAMHD1 activity through multiple means of regulation likely performs an important role in maintaining dNTP pools within a homeostatic range at each point in the cell cycle (Fig. 4). Future research into both identified and as of yet unidentified mechanisms of SAMHD1 post-translational regulation represents a potentially fruitful line of inquiry with implications for SAMHD1 biology and broader cellular processes.

SAMHD1, Cell Cycle Regulation, and Genomic Integrity.

Compared to its innate immune function, less attention has been given to the role of SAMHD1 in normal homeostatic cell maintenance. However, its role as a regulator of nucleotide metabolism may represent its primary biological function given the nearly ubiquitous expression of SAMHD1, the enzyme's regulation that is synchronized with changes in dNTP pools and cell cycle stage, and the fact that proper dNTP concentrations are essential for genomic integrity and DNA replication and repair.

SAMHD1 is widely established as a central regulator of dNTP pool dynamics within cells and as such its catalytic activity can directly influence the replicative capacity of the cell (97, 133–136). Silencing or degradation of SAMHD1 results in elevated dNTP pools and altered growth kinetics as evidenced by studies that demonstrate an increased retention of cells in the G_1 phase with a corresponding loss in S-phase cells (97, 133, 137). Intriguingly, the precise effect of knocking down SAMHD1 on proliferative capacity appears to depend on the specific cell type. Fibroblasts and THP-1 cells have been reported to grow either slower or faster, respectively, in the absence of SAMHD1 (97, 133). In THP-1 cells, the increased dNTP pools and enhanced proliferative capacity were accompanied by a reduction in spontaneous apoptosis (133). Conversely, up-regulation of SAMHD1 can also alter growth kinetics by contributing to a quiescent or differentiated phenotype in fibroblasts and THP-1 cells by coordinating with other nucleotide metabolizing enzymes to maintain reduced dNTP levels (97, 138). Similarly, overexpression of exogenous SAMHD1 results in reduced proliferation and increased apoptosis in HuT78 cells - a human T-cell lymphoma cell line - presumably by denying the cells the large quantities of dNTPs necessary to efficiently replicate their genomic DNA (139). These studies clearly identify SAMHD1 as a modulator of cellular growth kinetics, although additional research is required to quantify the mechanism and magnitude of the effect exerted by SAMHD1 activity.

Proper dNTP concentrations are also essential for genomic stability as imbalanced dNTP pools can hinder DNA replication and repair. By degrading dNTPs in resting or quiescent cells before they accumulate to levels that impede the efficiency or accuracy of the replication and repair machinery, SAMHD1 performs an essential function as a protector of genomic fidelity. Data from patients expressing inactive mutants of SAMHD1 underscore this point, as cells from these patients exhibit elevated dNTPs, growth arrest in G1, and hallmarks of response to DNA damage (137). These data suggest that SAMHD1 represents an important node in the cellular circuitry of tightly coordinated nucleotide synthesis and degradation that enables both proliferation and maintenance of genomic integrity. By integrating the myriad of transcriptional, translational, and post-translational regulatory mechanisms the cell can calibrate SAMHD1 activity to meet the precise metabolic needs of the specific cell cycle phase. Despite being implicated in such central processes, this aspect of SAMHD1 biology is still relatively under examined. Future work defining the role SAMHD1 plays in promoting cellular homeostasis through its effect on nucleotide pools, and the regulatory pathways that alter its activity, will likely yield important insights into the underlying mechanisms that control nucleotide metabolism and cell cycle progression, as well as the pathogenic phenotypes that result from their dysregulation.

SAMHD1 as an Effector of Innate Immunity

The discovery of SAMHD1 as an IFN1 inducible protein in dendritic cells hinted at the importance of SAMHD1 as an effector of innate immunity from the moment of its first discovery. Accordingly, virologist and immunologist have been responsible for many of the most significant advances to the understanding of SAMHD1 biology. While the following section briefly reviews these discoveries and the role of SAMHD1 as an effector of innate immunity, a recently published review exclusively explores the relationship between SAMHD1 and the innate antiviral response in greater detail (140).

SAMHD1 has garnered significant attention for its antiviral properties in non-dividing cells of hematopoietic lineage, including macrophages, dendritic cells, and resting CD4+T-cells (146, 147, 150). In these cells it is constitutively expressed and present in the dephosphorylated state, where it contributes to the maintenance of dNTP levels that are several hundred fold lower than in actively cycling CD4+ T-cells (141). Interestingly, the presence of dephosphorylated SAMHD1 in these cells coincides with the capacity of non-dividing hematopoietic cells to restrict efficient HIV-1 infection (101, 142–145). HIV-2 however, which carries the virulence accessory protein, Vpx, is able to efficiently transduce non-dividing hematopoietic cells. Incorporation of Vpx into HIV-1 virions relieved the restrictive phenotype, and suggested the presence of a specific cellular immune factor antagonized by Vpx (146–148). It was eventually revealed that SAMHD1 was the HIV cellular restriction factor counteracted by Vpx (143, 144). Through its dNTPase functionality, SAMHD1 is proposed to inhibit productive viral infection by reducing dNTP pools below the concentration required for efficient catalysis by viral DNA polymerases or reverse transcriptases (135, 149, 150). SAMHD1 thereby provides a kinetic block at the critical juncture where viral genomic content is replicated and incorporated into the host's genome. This block is reversible upon treatment with exogenous dNTPs or knockdown of SAMHD1 (135, 143, 144, 149). The importance of SAMHD1 dNTPase activity as a barrier against viral infection was further underscored by the finding that primary monocytes deficient for SAMHD1 due to genetic mutation are highly susceptible to HIV-1 infection (145). Vpx specifically counteracts the SAMHD1 mediated depletion of cellular dNTPs to enable efficient viral infection. It accomplishes this by orchestrating the degradation of SAMHD1 (67, 143, 144, 151). Vpx facilitates the interaction of SAMHD1 with the ubiquitin ligase substrate adaptor molecule DCAF1 through the C-terminal region of SAMHD1 (152), promoting recruitment of SAMHD1 to the CRL4 ubiquitin ligase complex where it is ubiquitinylated and marked for proteosomal degradation (69, 143, 144, 153). The loss of SAMHD1 and subsequent increase in dNTPs is sufficient to permit productive viral infection for Vpx containing virions.

Intriguingly, of the two viral subtypes, HIV-2 is the less virulent. Why this is the case is not entirely understood, but it has been proposed that by using Vpx to degrade SAMHD1 and enable productive infection of macrophages and dendritic cells, which serve as the sentinel cells of the immune system, HIV-2 may in fact be alerting the host's natural defenses to its presence. HIV-1 restriction in non-dividing immune cells may enable it to maintain an undetectable reservoir of latent virus, while avoiding activation of the host's immune systems (154–156). Evidence supporting this model shows that SAMHD1 restriction of

HIV-1 limits the innate and adaptive immune responses by preventing the activation of the cGAS/STING pathway (157). Inhibitors of SAMHD1 may therefore represent an important therapeutic tool for facilitating infection of myeloid cells and activating a robust immune response to HIV-1 infection (158).

Additional studies have broadened the scope of SAMHD1 innate immune functionality by demonstrating its antiviral restrictive capacity extends beyond HIV-1 to other retroviruses and DNA viruses such as herpes viruses (HSV-1) and hepatitis B (HBV) (85, 144, 149, 159–165). This strategy of warding off invasive pathogens through depletion of precursor metabolites is not a novel approach (150), as it finds precedence in bacteria such as *Eschericia coli* which express a dGTPase that reduces susceptibility to T7 bacteriophage infection (58, 166). Therapeutically targeting nucleic acid metabolizing enzymes in order to deplete intracellular dNTP pools is also an approach implemented by modern medicine in order to counter viral infection and cancer (167, 168).

More recently however, dNTP depletion has come under question as being fully sufficient to explain the entirety of SAMHD1's antiviral restriction capacity (169). Evidence exists to suggest that tetramerization deficient SAMHD1 enzymes may still be able to exert antiviral effects (129, 170). Additionally, the antiviral capacity of SAMHD1 is strictly correlated with its phosphorylation status on its C-terminus at T592, even while debate as to the actual effect of P-T592 on SAMHD1 catalytic activity persists. As previously discussed, SAMHD1 is phosphorylated in cycling cells at T592 in a cell cycle dependent manner, but dephosphorylated in most non-dividing hematopoietic cells where it is also able to efficiently restrict HIV-1 infection (93, 98, 101, 117, 120, 142). In addition to quiescence or differentiation, viral challenge, cytokine signaling (Il-12 and Il-18), or IFN1 treatment also result in the loss of SAMHD1 phosphorylation at T592 (98, 102, 109, 110). The loss of phosphorylation at T592 coincides with the reemergence of a cellular phenotype that is refractory to HIV-1 infection and provides a clear linkage between SAMHD1 and innate immunity, while emphasizing the importance of SAMHD1 phosphorylation status as a determinant of viral restriction. While phosphorylation of T592 has been established as coinciding with the ablation of the viral restriction capacity, some data suggest that this loss of antiviral capacity is not entirely coupled to diminished SAMHD1 catalytic activity (116, 117, 125, 169). Cells expressing phosphomimetic T592D or T592E mutations support this model, as they are unable to restrict viral infection but do not exhibit elevated dNTP pools or reduced dNTPase activity (81, 116, 169). The implication of this is that SAMHD1 is able to restrict viral infection through both its dNTPase activity as well as a putative yet to be discovered mechanism, the potency of which is dependent on the phosphorylation status of the enzyme at T592. The precise mechanisms through which SAMHD1 inhibits viral infection and how post-translational modifications influence its restrictive capacity represent important research questions going forward. The answers to these questions will further reveal the role of SAMHD1 in innate immunity, as well as potential opportunities to develop therapeutic strategies for mitigating the impact of viral infections.

SAMHD1 Mutations Result in Disease

Autoimmunity.

The central role SAMHD1 performs in nucleotide metabolism and immunity increases the probability that mutations to SAMHD1 will result in disease. Many mutations to SAMHD1 have been identified and are associated with several different disease phenotypes (Fig. 5). One of these diseases is the Type I interferonopathy Aicardi-Goutieres Syndrome (AGS) – a genetically determined autoimmune disease linked to aberrant nucleic acid processing (171–173). AGS is an autosomal genetic disorder that mimics the sequela of an *in utero* viral infection and retains significant overlap in phenotypic presentation with that of systemic lupus erythematosus (SLE) (172, 174–176). AGS is characterized by encephalopathy, leukodystrophy, calcifications of the basal ganglia, psychomotor retardation, cerebrospinal fluid lymphocytosis, and an over-production of interferon-α. Approximately 40% of the cases result in early childhood death (177).

AGS is a genetically heterogeneous disease, with mutations to SAMHD1 accounting for approximately 13% of all documented cases (177). Its etiology can be traced to mutations in SAMHD1 and 4 other enzymes involved in nucleic acid processing, TREX1, RNase H2, ADAR1, and MDA5 (52, 177–182). Loss-of-function mutations to these enzymes may result in the cytosolic accumulation of unprocessed nucleic acids that mimic invading pathogens. Unprocessed nucleic acids can then activate endogenous nucleic acid sensing pathways and result in subsequent interferon production. The common functionality of nucleic acid metabolism which links the causative AGS enzymes has led to the hypothesis that they play a role in suppressing antigenic nucleic acid by-products. The source of the antigenic nucleic acids however is unknown, and may vary by implicated enzyme. Conjectures as to how SAMHD1 negatively regulates interferon pathways have ranged widely - from suppression of retroelement activation to control of anomalous nucleic acid species resulting from genomic instability and altered DNA replication and repair (137, 183–185). Interestingly, AGS is commonly associated with pathologies of the nervous system - a system which given the specific requirements for rapid neurogenesis in early development and neuronal longevity make it especially susceptible to replication stress and impeded DNA repair pathways (186).

The phenotypic presentation of SAMHD1 associated AGS has several novel features not observed in other AGS associated genotypes, including cerebral vasculopathy, arthropathy, and mitochondrial DNA deletions (187–190). The clinical presentation of SAMHD1 induced AGS may therefore provide clues to the mechanism through which SAMHD1 contributes to nucleotide homeostasis and negatively regulates innate immunity. Attempts to recapitulate an AGS phenotype in SAMHD1 null mice have proven perplexing however, as SAMHD1 knockout mice exhibit elevated interferon levels but do not develop autoimmune disease (161, 191). A more promising animal system for modeling SAMHD1 induced AGS might be found in zebra fish. In this alternative to mouse models, zebra fish exhibit similar interferon overexpression and cerebrovascular pathologies upon deletion of SAMHD1 to those clinically observed in AGS patients (192).

Cancer.

Ample evidence exists to connect dNTP pool dysregulation to cancer and genomic instability (40). Elevated or imbalanced dNTP pools can result in a mutator phenotype (25, 193, 194) that disrupt genomic integrity and DNA replication and repair (195–197). Conversely, dNTP pool depletion can result in genomic instability that progresses to cancer (198). Additionally, an imbalance to dNTP pools can lead to loss of genomic fidelity and impaired replication efficiency and accuracy (27–29, 199). It is therefore no surprise that recent studies have begun to implicate SAMHD1 in various cancers, including lymphocytic leukemia, lung adenocarcinoma, and colon cancer (106, 200–202) (Fig. 5). The Catalogue of Somatic Mutations in Cancer (COSMIC) has recorded 164 unique mutations to SAMHD1 found in samples obtained from various cancer tissues (203). Mutations to SAMHD1 likely result in an imbalanced dNTP pools and create the prerequisite conditions for mutagenesis and genomic instability (40, 204). It is also possible that SAMHD1 prevents mutations by sanitizing nucleotide pools via degrading base modified dNTPs before they are incorporated into DNA (205, 206). Given its role in the maintenance of genomic stability, SAMHD1 may potentially perform an additional function in cells as a tumor suppressor enzyme. It will be important to determine if mutations to SAMHD1 are foundational in that they drive tumorigenicity, or if cancer cells must down-regulate the restrictive effect of SAMHD1 in order to supply themselves with the metabolites necessary for unconstrained growth.

Lastly, SAMHD1 will likely be important in targeted health therapies, as nucleotide analogue therapeutics are a common tool used in treatment of cancer and viral infections (207, 208). Following phosphorylation by intracellular kinases, these analogues are structurally similar to the endogenous dNTP substrate, and several are substrates for SAMHD1 (209). Most notably, Ara-C, a first line therapeutic regimen against acute myelogenous leukemia (AML), is degraded by SAMHD1 in cells (210–212). This minimizes the efficacy of the treatment to such an extent that SAMHD1 expression levels were negatively correlated with Ara-C treatment success in individuals with AML. Additionally, SAMHD1 appears to reduce the efficacy of thymidine based analogs used to treat HIV, and depletion of SAMHD1 from monocyte cells affects the susceptibility of HIV-1 infections to nucleoside reverse transcriptase inhibitors (79, 213, 214). Based on these finding, the development of a robust SAMHD1 inhibitor that can potentiate nucleotide analogue therapeutic regimens should become a priority for SAMHD1 researchers. Several groups have developed high throughput assays (215, 216), but to date, no potent inhibitor of SAMHD1 has been identified.

Open Questions

Since its discovery as a participant in innate immunity and as an HIV restriction factor, SAMHD1 has been the target of significant research efforts that have extensively detailed the fundamental biochemistry and cell biology of SAMHD1. However, important questions related to SAMHD1 biology remain. In a broad context, the centrality of SAMHD1 to cellular homeostasis is becoming apparent. SAMHD1 is a vital cog in the well-oiled cellular machinery that strictly controls the anabolic and catabolic pathways that determine cellular nucleotide content. By degrading dNTPs SAMHD1 fulfills important roles as a sentinel of

genomic integrity, a regulator of cell cycle progression, and an effector of innate and autoimmunity. Uncovering the details of SAMHD1 function and regulation in normal cells will provide insight into how its dysfunction leads to disease. Continued efforts to elucidate the *in vivo* mechanisms of regulation will be important for determining the enzyme's operation in the intricate and dynamic pathway of nucleotide metabolism. How post-translational modifications, such as phosphorylation and oxidation, coordinate with protein activation, localization, and oligomerization to tune SAMHD1 activity and maintain dNTP homeostasis is yet to be determined. Additionally, the biological function of SAMHD1 nucleic acid interaction is an important question. Is this a potential mechanism for viral restriction, or is it primarily related to the recently discovered capacity of SAMHD1 to promote DNA end resection during homologous recombination? Given that the facilitation of DNA repair by SAMHD1 represents a novel function of the enzyme unrelated to its catalytic activity, are there additional cellular actions SAMHD1 performs that are yet to be discovered? Along the same lines, understanding the biology of the SAM domain and SAMHD1 interactions with other proteins remains an open line of inquiry. In the context of disease, the comprehensive methods of viral restriction appears to be incompletely described, as does the precise manner in which SAMHD1 acts as a negative regulator of interferon signaling. Information about the role of SAMHD1 in disease, specifically cancer and autoimmunity, is in its nascent stages, but each new discovery contributes to our knowledge and presents potential translational opportunities.

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Abbreviations

AGS	Aicardi-Goutieres syndrome
CDKs	Cyclin Dependent Kinases
DCIP	dendritic cell derived IFN-γ induced protein
dATP	deoxyadenosine triphosphate
dGTP	deoxyguanosine triphosphate
dNDP	deoxynucleotide diphosphate
dNTP	deoxynucleotide triphosphate
H_2O_2	hydrogen peroxide
IFN1	Type-1 Interferon
RS1	regulatory site 1
RS2	regulatory site 2

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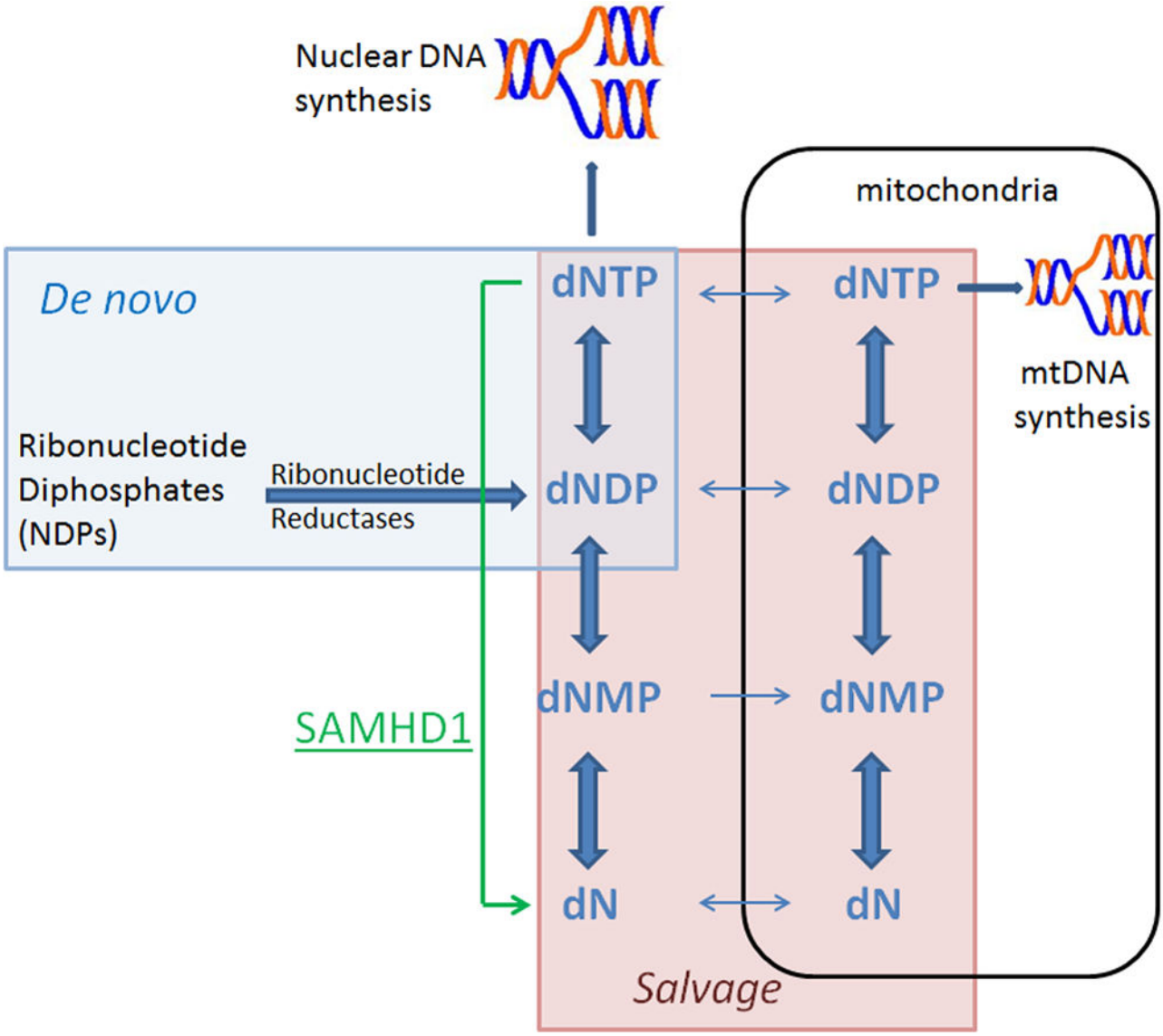

Figure 1. Overview of dNTP metabolism pathways and enzymes.

The *de novo* pathway of dNTP synthesis is shaded blue. The salvage pathway shaded in red consists of complementary pathways in the cytosol and mitochondria. Cellular kinases phosphorylate deoxynucleosides (dN) and deoxynucleotides (dNMP, dNDP), while 5'-deoxynucleotidases and phosphorylases catalyze the opposing reactions which degrade nucleotides to help maintain a homeostatic balance. The SAMHD1 triphosphohydrolase reaction is highlighted in green.

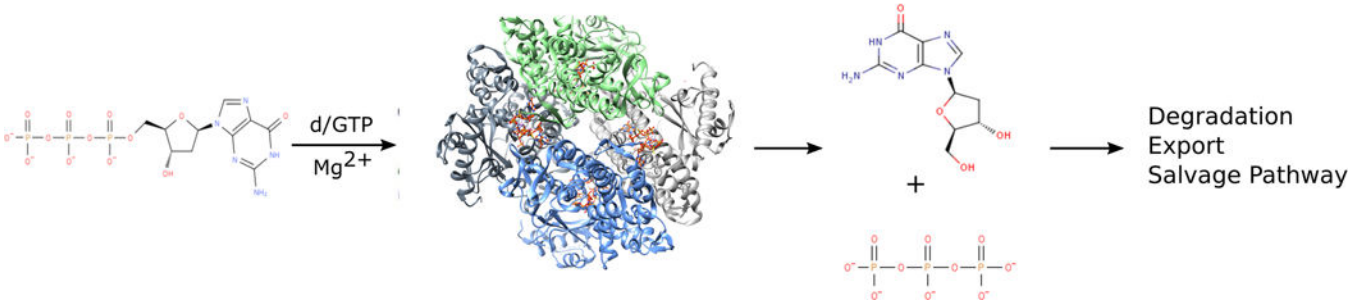

Figure 2. SAMHD1 is a deoxynucleotide triphosphohydrolase.

SAMHD1 hydrolyzes dNTPs in the presence of activating nucleotides and divalent metal cations into their cognate nucleoside and inorganic tripolyphosphate. Nucleosides are then degraded further, exported from the cell, or recycled through the nucleotide salvage pathway.

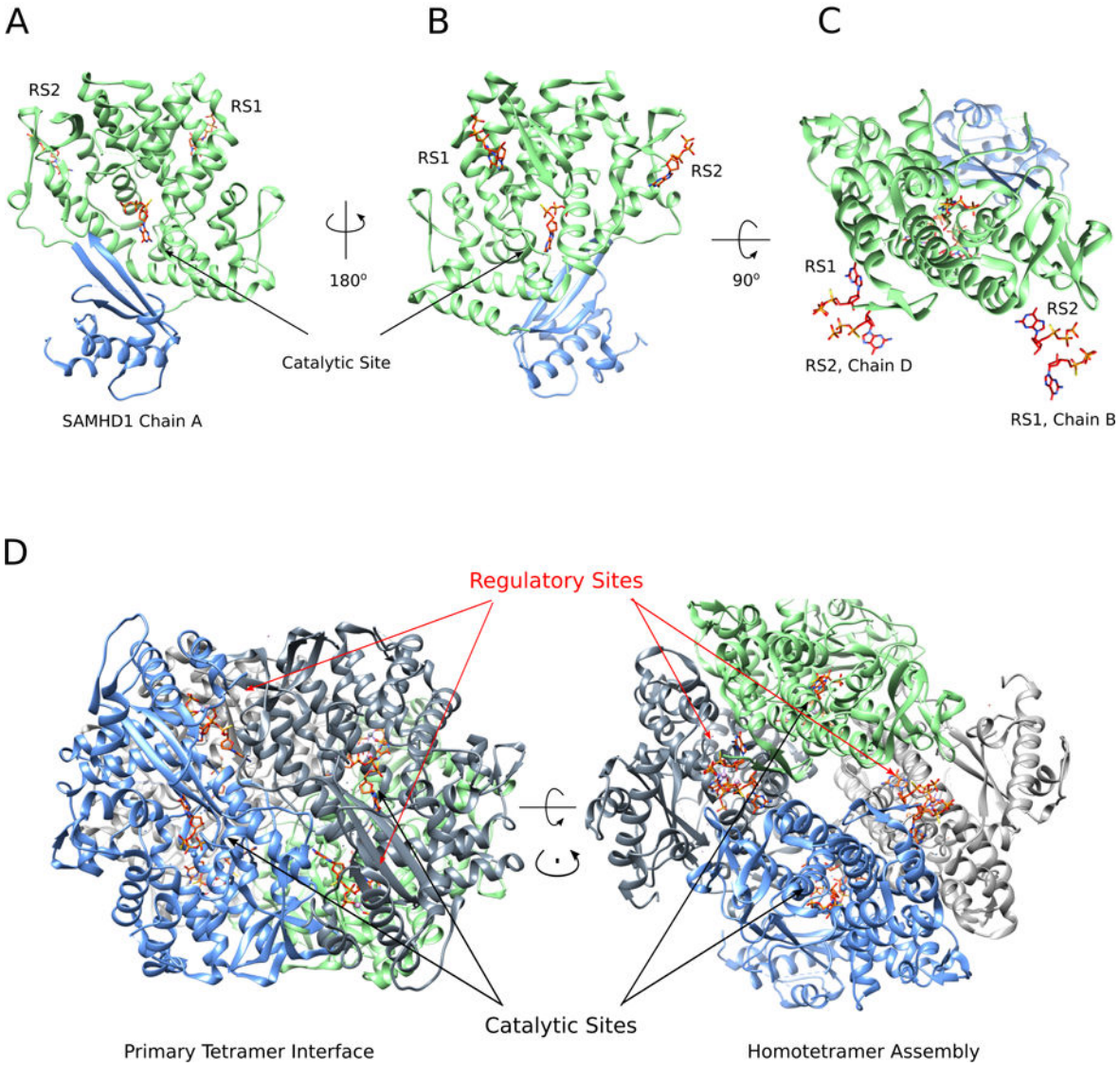

Figure 3. The sequential binding of regulatory nucleotides drives SAMHD1 tetramerization and catalytic activation.

(A, B) SAMHD1 monomer depicting the HD domain major lobe (green) and C-terminal region (blue) (PDBID: 4BZC (71)). The catalytic site and regulatory site 1 (RS1) and 2 (RS2) are indicated with bound dGTP (C) SAMHD1 monomer as in A and B, with paired nucleotides from the tetrameric regulatory cleft. Each cleft contains two regulatory nucleotide binding sites from adjacent monomers that stabilize subunit interactions. (D) The catalytically active tetrameric holoenzyme of SAMHD1 reveals the primary tetramer interface (left) and the homotetrameric assembly (right).

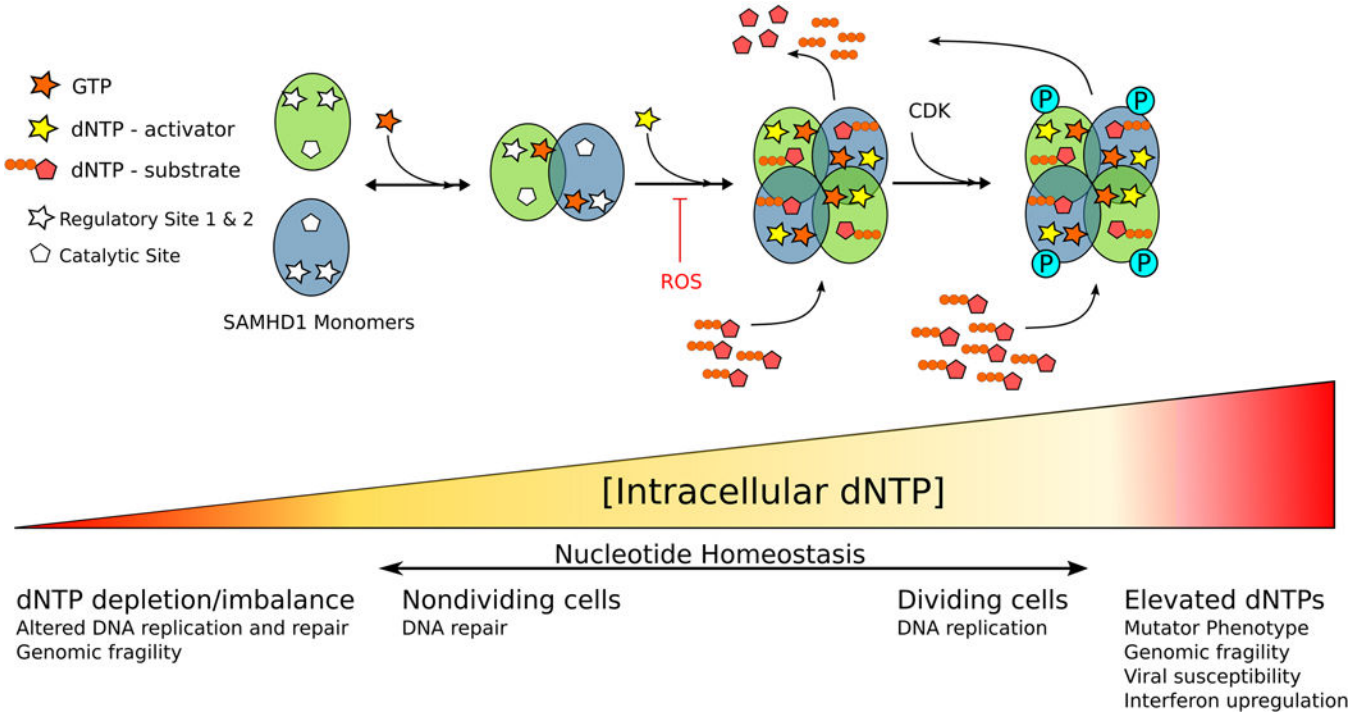

Figure 4. SAMHD1 catalytic activity is tightly controlled by regulatory nucleotides and essential for the maintenance of nucleotide homeostasis.

Under conditions of low dNTPs, SAMHD1 exists in a monomer-dimer equilibrium. Binding of GTP in RS1 stabilizes the dimer conformation. Elevation of intracellular dNTP concentrations above the activation threshold (1–20μM) results in dNTPs binding at RS2 and SAMHD1 tetramerization. Tetrameric SAMHD1 is able to catalyze the degradation of dNTPs and thereby prevent accumulation to levels that would be cytotoxic. Phosphorylation is proposed to destabilize tetramer stability without modifying catalytic efficiency, thereby allowing for an increase in dNTP pools necessary for DNA replication without creating mutagenic dNTP conditions.

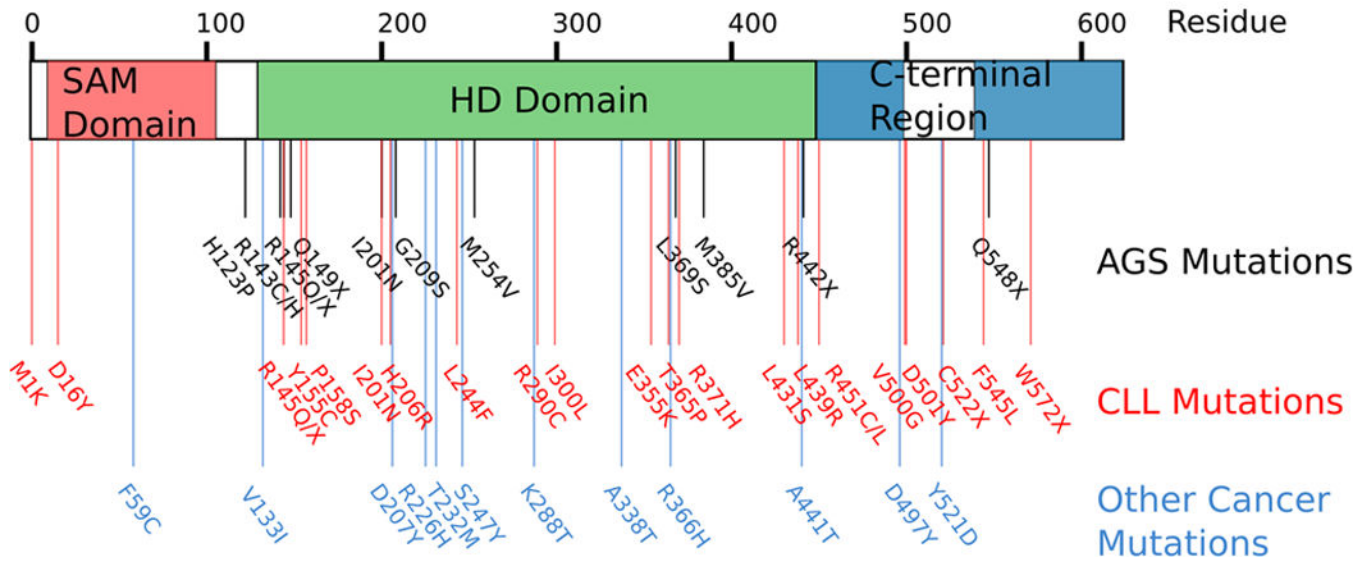

Figure 5. SAMHD1 gene schematic depicting location of AGS and Cancer inducing mutations.

SAMHD1 consists of an N-terminal Sterile Alpha Motif domain (red), a catalytic HD domain (green), and a distinct C-terminal region. Mutations in each region have been identified in patients with autoimmune disorders and cancer (178, 200, 201, 204). AGS mutations are believed to be causative loss-of-function resulting in dysregulation of nucleotide metabolism. Questions remain as to whether SAMHD1 mutations found in cancer cells are foundational oncogenic events, secondary promoters of tumorigenesis, or symptoms of genome instability.