

SAMHD1: mechanisms of regulation and viral evasion

Ferdinand Roesch

Division of Human Biology and Basic Sciences, Fred Hutchinson Cancer Research Center
1100 Fairview Ave. N.,
Seattle, WA 98109, USA
<froesch@fredhutch.org>

Abstract. Sterile alpha motif and histidine-aspartate domain-containing protein 1 (SAMHD1) is a restriction factor blocking replication of many viruses, including human immunodeficiency virus (HIV). SAMHD1 was initially identified by homology with a murine GTPase induced by interferon gamma (IFN γ) and known for its involvement in Aicardi-Goutières syndrome (AGS), a rare inflammatory disorder [1]. In 2011, the identification of SAMHD1 as the restriction factor inhibiting HIV-1 infection in macrophages and dendritic cells has been a major advance in the field of retrovirology [2, 3]. In this review, I will discuss recent advances on the mechanism of SAMHD1 restriction of HIV-1, the regulation of SAMHD1 by the cell cycle and by cytokines, and how viruses evolved to counteract SAMHD1 restriction.

Key words : HIV-1, SAMHD1, cytokines, cell cycle, innate immunity

Résumé. SAMHD1 (*Sterile alpha motif and histidine-aspartate domain-containing protein 1*) est un facteur de restriction bloquant la réplication de nombreux virus, dont le virus de l'immunodéficience humaine (VIH). SAMHD1 a été initialement identifié par homologie avec une GTPase murine induite par l'interféron gamma (IFN) et était connu pour son implication dans le syndrome Aicardi-Goutières (AGS), une maladie inflammatoire rare [1]. En 2011, l'identification de SAMHD1 comme étant le facteur de restriction bloquant l'infection par le VIH-1 dans les macrophages et les cellules dendritiques a été une avancée majeure dans le domaine de la rétrovirologie [2, 3]. Dans cette revue, je vais discuter les avancées récentes de la recherche concernant le mécanisme de restriction par SAMHD1, la régulation de SAMHD1 par le cycle cellulaire et les cytokines, et les mécanismes d'évolution virale permettant de contrecarrer l'action de SAMHD1.

Mots clés : VIH-1, cycle cellulaire, cytokines, immunité innée

AGS and nucleic acid metabolism

Aicardi-Goutières syndrome (AGS) is an early onset autoimmune condition causing encephalopathies in infants [1]. This inflammatory disorder is characterized by aberrant secretion of type I interferon (IFN-I) and induction of IFN stimulated genes (ISGs), which are usually hallmarks of congenital infection. To date, genetic mutations in 7 genes have been linked to AGS: TREX1; RNASEH2 A, B and C; SAMHD1; ADAR and MDA5 [4]. All of these genes have functions in nucleic acid metabolism or immune sensing, suggesting that they may inhibit the generation or detection of immunostimulatory nucleic acid species. Inter-

estingly, several of the genes involved in AGS have also been reported to influence HIV-1 replication (*table 1*).

The precise mechanisms triggering AGS are not completely elucidated yet, and mutations in different genes may cause AGS in different ways. However, one emerging model is that the aberrant IFN synthesis observed in patients is caused by uncontrolled replication of endogenous mobile elements and subsequent detection by the innate immune system. For instance, mutations in TREX1 and SAMHD1 correlate with increased LINE-1 and Alu/SVA retrotransposition [14, 15]. As a consequence of the replication of these retroelements, nucleic acid may accumulate in the cytoplasm and be recognized by RNA or DNA sensors. The identity of the sensor(s) responsible for this detection is currently under characterization for the different AGS genes. MDA5, which has directly been implicated in AGS,

Corresponding author : F. Roesch

Table 1 AGS genes are involved in nucleic acid metabolism and HIV replication.

Gene	Symbol	Function	Role	References
<i>Three prime repair exonuclease 1</i>	<i>TREX1</i>	3' exonuclease involved in DNA repair	Degrades HIV-1 DNA after reverse transcription, limits viral sensing	[5]
<i>Ribonuclease H2 subunit A</i>	<i>RNASEH2A</i>	Catalytic subunit RNASEH2, involved in RNA degradation in RNA:DNA hybrids	Promotes HIV-1 replication	[6, 7]
<i>Ribonuclease H2 subunit B</i>	<i>RNASEH2B</i>	Regulatory subunit of RNASEH2		[6]
<i>Ribonuclease H2 subunit C</i>	<i>RNASEH2C</i>	Regulatory subunit of RNASEH2		[6]
<i>Sterile alpha motif and histidine-aspartate domain-containing protein 1</i>	<i>SAMHD1</i>	Reduces dNTPs pool in quiescent cells	Restricts HIV-1 reverse transcription by dNTP starvation	[2-3, 8-10]
<i>Adenosine deaminase, RNA specific</i>	<i>ADAR</i>	Involved in RNA editing and important for suppression of IFN signaling	Stimulates HIV-1 protein expression and viral production	[1, 11]
<i>Interferon induced with helicase C domain 1</i>	<i>IFIH1</i> <i>MDA5</i>	DEAD box RNA helicase detecting cytoplasmic RNAs from many viruses	Identified in an overexpression screen for ISGs restricting HIV	[12, 13]

recognizes Alu double stranded RNAs when mutated [16]. In SAMHD1 depleted cells, RNA species are detected in a process regulated by the Akt/PI3K pathway [17], and single stranded DNA fragments released from stalled forks of replication activate the cGAS/STING pathway [18]. Cyclic GMP-AMP synthase (cGAS) may play a central role in the establishment of AGS. Indeed, recent studies using knockout mouse models demonstrated that depletion of RNASEH2B [19] and TREX1 [20] lead to the development of an inflammatory response only in presence of cGAS. Ultimately, the abnormal IFN production may contribute to trigger encephalopathies and the other neurological disorders observed in AGS patients.

Antiviral activity of SAMHD1

HIV-1 primarily infects activated CD4+ T cells. In comparison, quiescent cells, such as macrophages, dendritic cells or resting CD4+ T cells, are relatively resistant to HIV-1 infection. This has been linked to a post-entry restriction at the step of reverse transcription, which can be abrogated by the viral protein Vpx [21-23]. This protein is encoded by HIV-2 and some strains of simian immunodeficiency virus (SIV) strains and recruits the DDB1/DCAF1/Cul4a E3 ubiquitin ligase complex, allowing it to target the restriction factor to proteasomal degradation. SAMHD1 was identified as this

restriction factor by two separate groups in 2011 [2, 3]. Rather than targeting a specific component of the virus, SAMHD1 creates a “hostile environment” for infection by lowering the amounts of available nucleotides (dNTPs), ultimately blocking reverse transcription. This is achieved through SAMHD1’s deoxynucleoside triphosphate triphosphohydrolase (dNTPase) enzymatic activity [9]. Several studies have demonstrated the importance of this activity for the antiviral effect of SAMHD1. For instance, exogenous addition of deoxynucleosides to the medium (that are converted in dNTPs in the cell) rescues infection even in presence of SAMHD1 [8], while drugs depleting dNTPs pools such as hydroxyurea inhibit HIV-1 replication [24]. Consistent with this, SAMHD1 restricts replication of other retroviruses [25] and of DNA viruses like *hepatitis B virus* (HBV), *vaccinia* and *herpes simplex virus type 1* [26, 27] through dNTP starvation.

In addition to this antiviral effect through nucleotide starvation, some groups reported dNTPase-independent mechanisms of restriction, in particular involving a putative exonuclease activity [28, 29]. These observations are highly controversial, as they have not been reproduced by other groups, which suggested they were artefacts from the co-purification of a contaminant nuclease [30, 31]. However, some SAMHD1 mutants unable to tetramerize or hydrolyze dNTPs still retain some antiviral activity [32], suggesting that other mechanisms of restriction may exist.

A recent report indicated that SAMHD1 suppresses HIV-1 LTR-driven gene expression and may potentially regulate viral latency [33].

Viral antagonism of SAMHD1

Evolutionary analyses indicated that SAMHD1 is evolving under strong positive selection in primates [34, 35], which is a sign of genetic conflict between hosts and pathogens. As a consequence, viruses have evolved ways to counteract or bypass SAMHD1 restriction. Viruses of the HIV-2/SIV_{SM} clade encode Vpx, which targets SAMHD1 for proteasomal degradation. This function originally emerged in the related viral protein Vpr, before a recombination or duplication event gave birth to Vpx, which took over SAMHD1 antagonism. Indeed, viruses of the SIV_{AGM}, SIV_{DEB} and SIV_{MUS} clades, which do not encode Vpx, are all able to antagonize SAMHD1 through Vpr [34]. Vpx/Vpr and SAMHD1 are engaged in an evolutionary arms race, where evolution in SAMHD1 to evade degradation is met by adaptation in Vpx/Vpr that restores the ability to antagonize the antiviral protein. Consistent with this model, toggling of the Vpx/Vpr interaction interface has been described, with some Vpx/Vpr proteins binding SAMHD1 through its C-terminal domain, and other recognizing the N-terminus [36]. Viral antagonism by Vpx/Vpr proteins can also be highly species specific: for example, in African Green Monkeys, SAMHD1 proteins from each subspecies are targeted for degradation by Vpr proteins from their cognate viruses, but not from all other ones [37]. These studies demonstrated that for most lentiviruses, antagonizing SAMHD1 is absolutely crucial for viral fitness.

HIV-1, the exception to the rule?

HIV-1, however, seems to be an exception to this rule. Indeed, HIV-1 is unable to degrade SAMHD1. The complex evolutionary history of HIV-1 may explain this lack of SAMHD1 antagonism (*figure 1*). HIV-1 originated from a cross-species transmission event of SIV_{CPZ} to humans, which itself is the result of recombination between SIV_{RCM} and a virus from the SIV_{MUS} clade [38]. During this recombination event, a new Vif protein was created, which gained the ability to counteract APOBEC3 proteins from chimpanzees and humans, giving SIV_{CPZ} a selective advantage likely contributing to its ability to jump host species [39]. However, this recombination also led to the loss of Vpx, leaving SIV_{CPZ} with a Vpr protein unable to degrade SAMHD1. In comparison, HIV-2, which derives

from SIV_{SM} and has no intermediate in chimpanzees, kept the Vpx gene. Strikingly, SAMHD1 antagonism did not evolve again in Vpr nor in any other HIV-1 protein.

Therefore, it appears that HIV-1 undertook a unique evolutionary path, since it has no viral countermeasure to SAMHD1 restriction but yet it displays a good viral fitness. It has been proposed that the lack of SAMHD1 degradation activity in HIV-1 is actually beneficial for the virus, allowing it to stay “under the radar” of the immune system [40]. Even if SAMHD1 degradation by Vpx does indeed lead to increased HIV-1 detection through cGAS [41], increased IFN production [42] and antigen presentation [43] in dendritic cells (DCs), this model might imply that there is direct benefit to lose the *vpx* gene. Nonetheless, once acquired, SAMHD1 antagonism has not been lost at any other point during lentiviral evolutionary history [34], and there is important selective pressure on viruses to counteract SAMHD1, as evidenced by species-specific adaptations in Vpr/Vpx maintaining SAMHD1 antagonism [36, 37].

There are other possible reasons explaining why HIV-1 did not regain SAMHD1 antagonism. For instance, the reverse transcriptase (RT) enzyme of HIV-1 may have evolved to accommodate particularly low levels of dNTPs. This hypothesis is supported by multiple biochemical studies that have shown that HIV-1 RT has a better affinity for dNTPs than RT proteins from other lentiviruses. In one study, the average values for the Michaelis constant (K_m) for HIV-1 strains RT were 10-fold lower than for HIV-2 and the SIV strains tested (0.179 vs. 1.79 μM on average) [44]. In line with these observations, a point mutation decreasing RT affinity for dNTPs dramatically reduced HIV-1 infectivity in macrophages [45], likely through increased SAMHD1 restriction [8]. Thus, due to the particularly high affinity of its RT, HIV-1 may perform reverse transcription even in conditions where nucleotides are scarce. In other cell types, such as terminally differentiated macrophages, HIV-1 may achieve infection by taking advantage of a G1-like state where SAMHD1 is inactive [46, 47]. Thus, HIV-1 may have compensated its lack of SAMHD1 antagonism by other mechanisms allowing infection of quiescent cells at low levels.

Although SAMHD1 plays an important role in restricting HIV infection in quiescent cells, there is substantial evidence for other potent blocks. For instance, HIV-2, which encodes Vpx, seems to be infecting DCs just as poorly as HIV-1 [48], even though high levels of infection by HIV-2 have been reported [49]. This has been linked with low surface levels of CD4, decreased viral fusion [50], and reduced interaction with CD169, an attachment factor important for trans-infection [51]. Infection in resting CD4⁺ T cells, another cell type where SAMHD1 is active against HIV

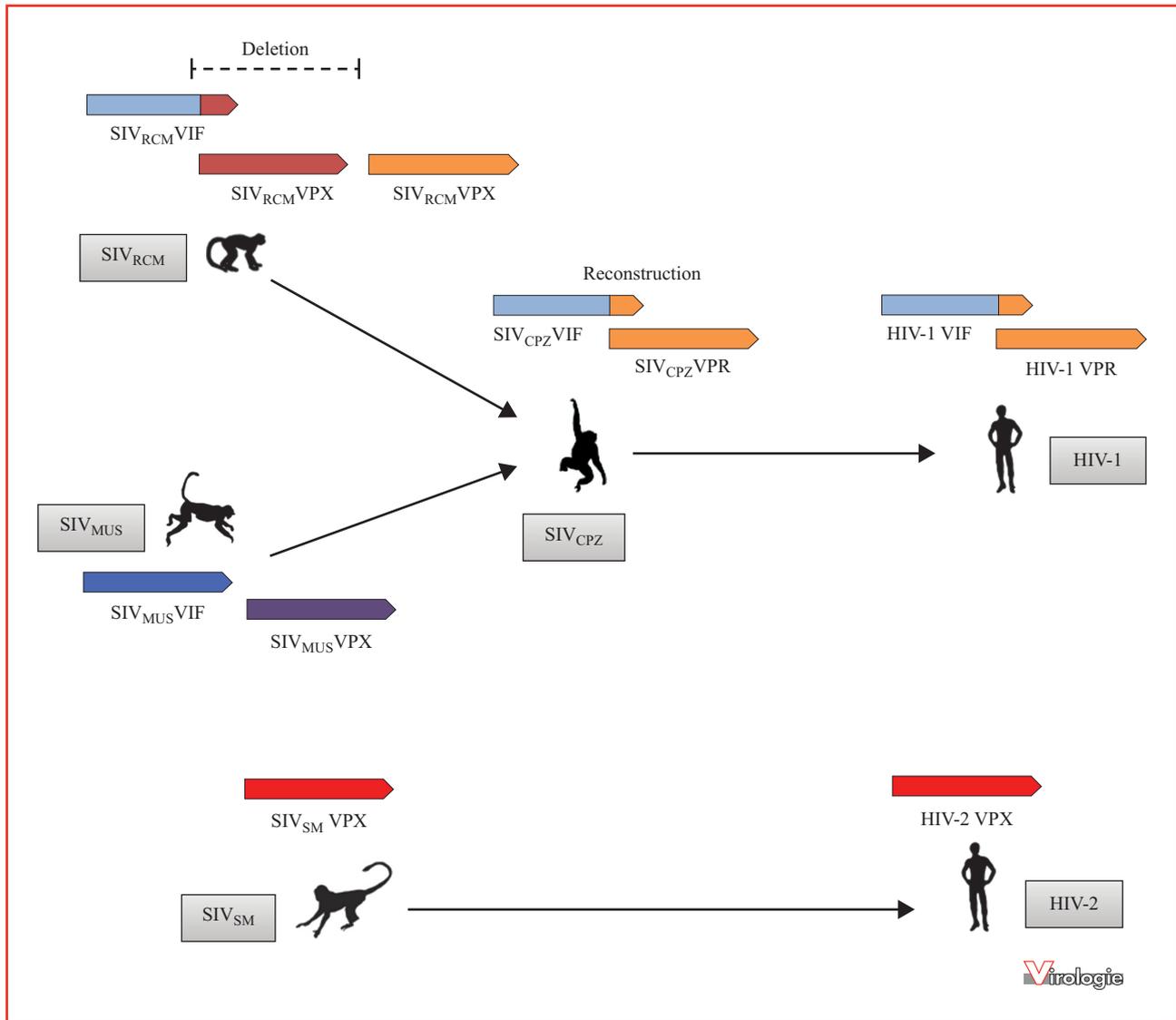


Figure 1. The evolutionary history of HIV-1 led to the loss of Vpx. HIV-1 is the result from cross-species transmissions from SIV_{CPZ}, a lentivirus infecting chimpanzees, while HIV-2 derives from SIV_{SM}, present in sooty mangabeys. SIV_{SM} encodes a functional vpx gene (red), which was kept in HIV-2. In contrast, SIV_{CPZ} does not encode Vpx, and its Vpr protein (orange) does not degrade SAMHD1. This is because SIV_{CPZ} was created by a recombination event between SIV_{RCM} and SIV_{MUS}, during which ≈ 380 bp encompassing the whole vpx gene of SIV_{RCM} and a part of vif were deleted. The C-terminal domain of Vif (which overlapped with Vpx) was reconstructed by overprinting, creating a new Vif (blue/orange) that was likely critical for viral adaptation to APOBEC3s in chimpanzees and humans.

[52], is severely restricted at the step of reverse transcription, integration and transcription [53, 54].

Structural regulation of SAMHD1

SAMHD1 is 626 amino acid protein (figure 2) and comprises 3 main domains:

- a catalytic HD domain, carrying the enzymatic activity;

- a conserved SAM domain which may be important for protein-protein interactions;
- and a C-terminal domain involved in nucleic acid binding, that is recognized by some Vpx from HIV-2/SIV_{SM} strains. SAMHD1 also has a nuclear localization signal (NLS) located at the N-terminus. Cytoplasmic mutants of SAMHD1 where this NLS is deleted are still enzymatically active, but resistant to degradation by Vpx and Vpr proteins [55].

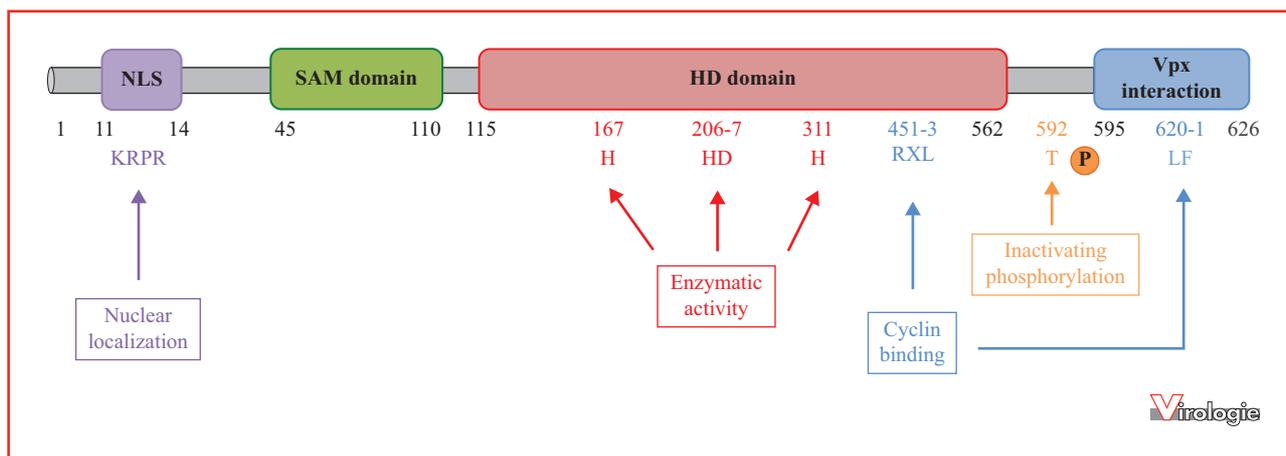


Figure 2. SAMHD1 domain organization. SAMHD1's main domains are represented: the nuclear localization signal (purple), the SAM domain (green), the catalytic HD domain (red) and the C-terminal domain interacting with SIV_{SM} Vpx (blue). Specific motifs and positions and their described functions are also indicated by arrows.

At low concentrations of dNTPs, SAMHD1 exists in a monomer-dimer equilibrium, which is inactive. When levels of dNTPs are high, dGTP serves as a primary substrate for SAMHD1. The protein then undergoes allosteric changes and tetramerizes to form the catalytically active form of the enzyme, able to hydrolyze all four dNTPs [56]. Thus, SAMHD1 enzymatic activity is regulated by oligomerization, which is itself influenced by the levels of dNTPs (and in particular of dGTP) in the cells.

Regulation of SAMHD1 by the cell cycle

Biosynthesis of dNTPs is accomplished through two complementary pathways: *de novo* synthesis, with the action of the key enzyme ribonucleotide reductase 2 (RNR2); and the salvage pathway, which recycles dNTPs from nucleic acid catabolism, and from the extracellular milieu. Cells need a sufficient supply of dNTPs to perform essential processes such as DNA replication and DNA repair, while avoiding nucleotide imbalance, which can be genotoxic due to increased mutation rates and genome instability. Therefore, dNTPs levels need to be tightly controlled, in particular throughout cell cycle progression. This is achieved by several mechanisms, such as temporal activation of the *de novo* synthesis pathway through regulation of RRM2, a regulatory subunit of RNR2 only expressed in cycling cells [57]. In contrast, the salvage pathway is constitutively active, allowing processes like DNA repair to take place in resting cells.

SAMHD1, through its dNTP hydrolase activity, is another powerful regulator of nucleotide levels. Although SAMHD1 expression can be regulated at the transcriptional level by methylation of its promoter [58], SAMHD1

protein is detected both in resting and cycling cells [59]. SAMHD1 enzymatic activity, however, is regulated by post-translational modifications (*figure 3*). Indeed, SAMHD1 phosphorylation on the Threonine residue at position 592 (T592) inactivates its activity [60, 61]. This post-translational modification is mainly carried out by Cyclin dependent kinase 1 (CDK1), which associates with cyclin A2 to control the G₁/S transition. Interaction with this complex is mediated by at least two motifs in SAMHD1 (*figure 2*): an RXL motif located in the HD domain [62, 63], and a conserved dihydrophobic motif in the C-terminal domain [64]. In addition to CDK1, cyclin A2 also associates with CDK2, which may phosphorylate SAMHD1 in primary cells [65]. Other cyclin/CDKs complexes, such as cyclinD2/CDK4 and cyclinD3/CDK6 [65, 66] were also reported to influence SAMHD1 phosphorylation in macrophages. Interestingly, p21, an inhibitor of CDK2, and p53, which acts upstream of p21, both influence HIV-1 replication in macrophages [67] through SAMHD1 phosphorylation and/or repression of RNR2 [68, 69]. Phosphorylation is thought to regulate SAMHD1 activity by reducing tetramer formation and dNTPase activity [64], although this model remains controversial [70]. Interestingly, the holoenzyme PP2A-B55 α has just been identified as the phosphatase mediating SAMHD1 dephosphorylation during mitotic exit [71].

Regulation of SAMHD1 by immune mediators

In addition to cell cycle progression, stimuli like cytokines also modulate SAMHD1 levels and activity (*figure 4*). For instance, IL-12 and IL-18 induce SAMHD1 expression

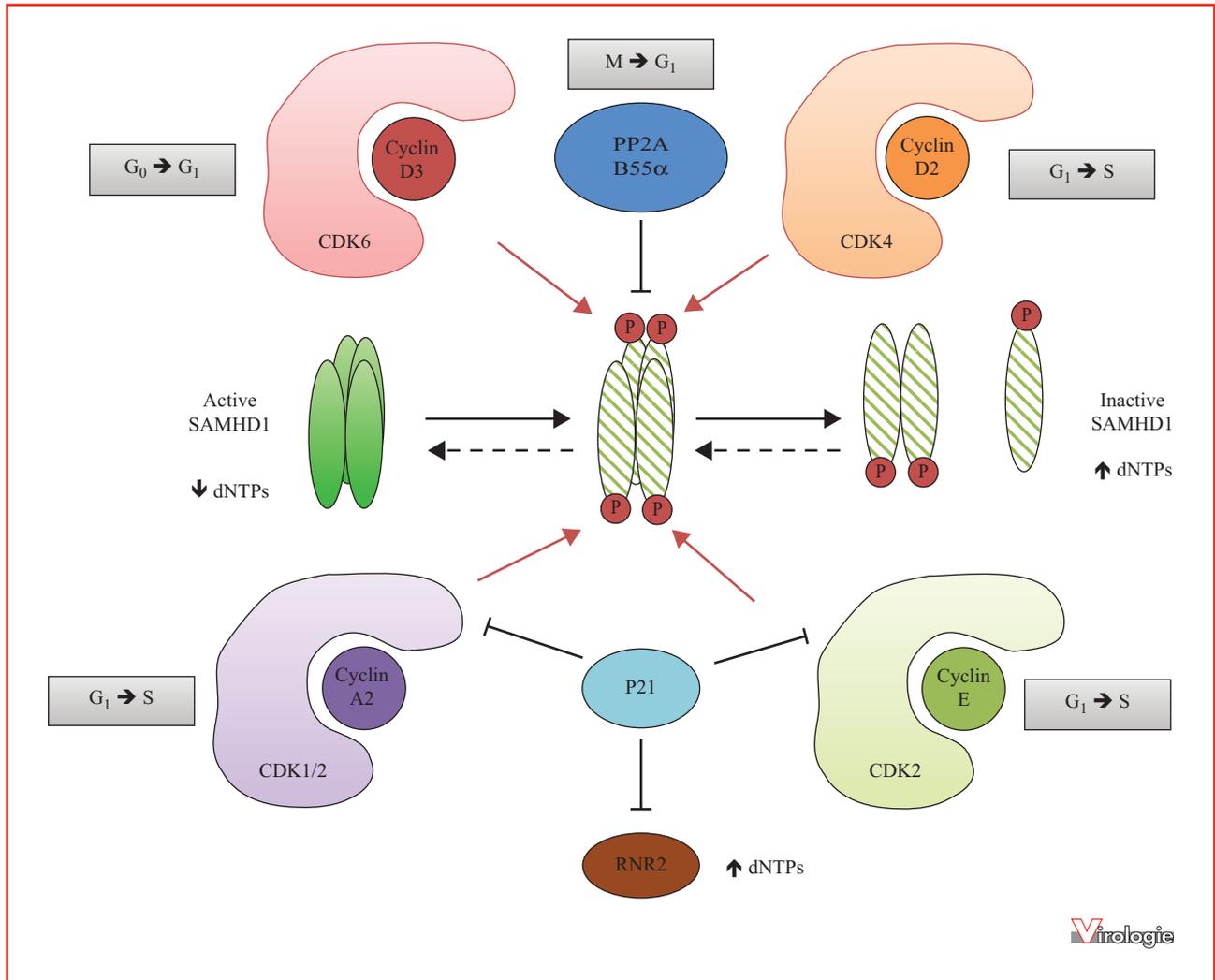


Figure 3. SAMHD1 regulation by the cell cycle. Cyclin/CDK complexes and other proteins regulating SAMHD1 activity are represented. The cell cycle transitions controlled by each complex are indicated in the grey boxes. All 4 complexes induce phosphorylation at the T592 residue, which leads to inactivation of the enzyme and loss of the tetrameric active state. P21, the natural inhibitor of the CDK2 kinase, also regulates dNTPs levels by inhibiting RNR2, a key enzyme in the *de novo* synthesis pathway. PP2a-B55 α is a phosphatase dephosphorylating SAMHD1.

in macrophages [72], while TLR9 stimulation upregulates SAMHD1 levels in peripheral blood lymphocytes [73]. Initial studies conducted in cell lines and monocytes indicated that IFN may enhance SAMHD1 expression by increasing IRF3-mediated transcription [74], and down-regulating micro-RNAs (miRs) targeting the 3' UTR of the SAMHD1 transcript [75]. However, this effect of IFN on SAMHD1 levels has not been recapitulated in primary macrophages, dendritic cells and primary T cells [59, 76]. These conflicting results may indicate that the effect of IFN and other cytokines on SAMHD1 expression may be cell type specific. SAMHD1 levels may also be regulated by cell activation and interaction with other immune cells.

For instance, SAMHD1 is down-modulated in dendritic cells following co-culture with lymphocytes, resulting in increased HIV replication, DC maturation and innate sensing [77, 78].

Rather than through an “on/off switch”, cytokines may fine-tune SAMHD1 activity by phosphorylation at the T592 residue. Type I interferon [60], IL-7 and IL-2 [79] have been reported to affect SAMHD1 phosphorylation, suggesting that this may be a successful strategy for the host to balance SAMHD1 antiviral effects with its constitutive functions. Finally, redox signaling may also regulate SAMHD1 enzymatic activity [80]: three cysteine residues forming an internal disulfide bond are indeed sensitive to

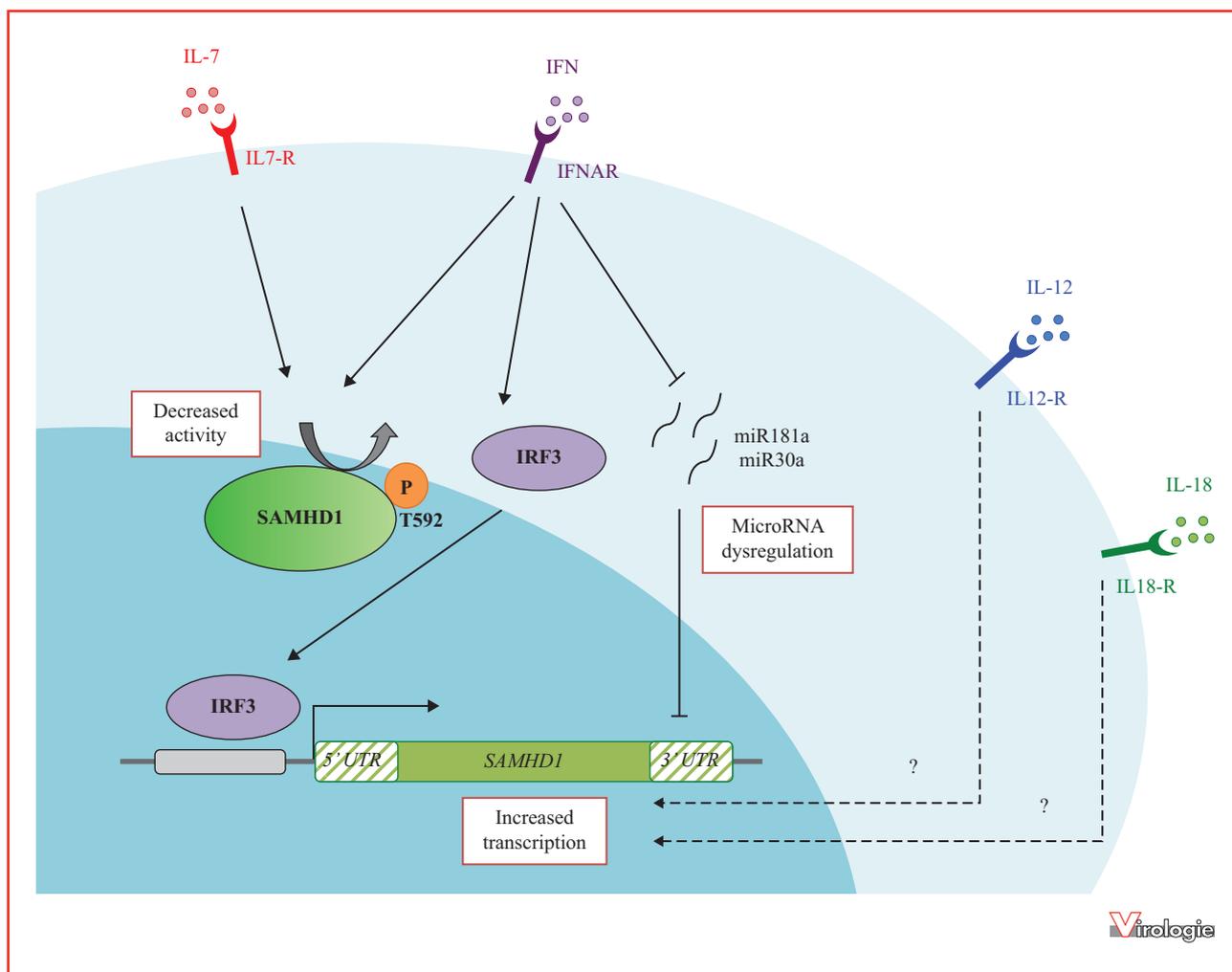


Figure 4. SAMHD1 regulation by cytokines. The effect of cytokines on SAMHD1 expression and activity is represented. IL-7 and IFN induce phosphorylation of SAMHD1, leading to its inactivation. IFN stimulation also decreases levels of two micro-RNAs (miRs) that target SAMHD1 3' UTR and promote IRF-3 mediated transcription. IL-12 and IL-18 stimulation lead to increase SAMHD1, presumably through enhanced transcription.

oxidation, which in turns impacts SAMHD1 tetramerization and subcellular localization.

SAMHD1 functions beyond viral restriction

The variety and subtlety of the mechanisms controlling SAMHD1 suggest that it fulfills crucial homeostatic activities. This is therefore not that surprising that mutations in SAMHD1 have been detected in many different types of cancer [81-83]. SAMHD1 may protect from cancer through its role in the DNA damage response: indeed, SAMHD1 expression is increased following DNA damage [84]. It has

been suggested that SAMHD1 helps DNA repair by homologous recombination following double strand breaks [85] and promotes the degradation of DNA at stalled replication forks through stimulation of the exonuclease MRE11 [18]. A broader role for SAMHD1 in adaptive and innate immunity has also been reported: SAMHD1 may enhance immunoglobulin hypermutation in B cells [86] and suppress innate immune responses through the IFN and NF κ B pathways [87]. These recent observations are very interesting, since they may suggest that SAMHD1 modulates immune responses against a wide range of viruses. Overall, these recent studies indicate that SAMHD1 has broader activities than originally anticipated, and could impact many cellular processes beyond HIV restriction and nucleotide metabolism.

Conclusion

By depleting the pools of nucleotides available to cells, SAMHD1 is a pleiotropic enzyme regulating key cellular processes such as DNA repair, genome stability, control of mobile elements, and innate immunity against many viruses. In the last few years, exciting research has started to uncover how the activity of SAMHD1 is fine-tuned during cell cycle progression, in specific cell types, or in response to extracellular stimuli. Inactivation of SAMHD1 by phosphorylation seems to be a particularly efficient strategy to quickly control the levels of dNTPs. It will be interesting to study how other post-translational modifications affect SAMHD1 activity, and to identify the cellular partners of SAMHD1 responsible for these effects. The recent discovery that SAMHD1 may have a broad impact on innate responses also raises new questions: is this new activity controlled by cell cycle progression, or somehow controlled by immune activation? Another question that remains open is how SAMHD1 mutants lacking dNTP hydrolysis are able to retain some activity. Finally, the interplay between SAMHD1 and HIV-1 is unique throughout lentiviral evolution, as unlike most other lentiviruses, HIV-1 is not able to degrade the antiviral protein. Understanding how HIV-1 adapted to such a powerful restriction factor may help inform the development of therapies using dNTP starvation as a strategy.

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Conflicts of interests : None.

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