Review

The role of SAMHD1 expression and its relation to HIV-2 (Vpx) gene production

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A R T I C L E   I N F O

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SAMHD1 (sterile alpha motif and HD domain 1) is a protein that is found in myeloid cells, which restricts HIV1 replication. It depletes the de-oxy-nucleoside tri-phosphate (dNTPs) pool needed for a viral cDNA synthesis leading to inhibition of viral replication inside the cells. However, it does not restrict HIV2 replication in myeloid cells due to the presence of viral Vpx protein. Vpx is a virion-associated protein which augments viral infectivity and it only exists in HIV2 and it has been recently shown in Simian Immunodeficiency Virus (SIV) and which can induce degradation of SAMHD1 protein. This increases the amount of dNTPs for viral reverse transcription in cytoplasm and HIV infection. HIV2 reverse transcription is believed to be less active than HIV1 and this could be the reason for the absence of Vpx from HIV1. Protein expression and interaction between Vpx and SAMHD1 remains unclear. The interaction of SAMHD1 and HIV2-VPx patients' cells can be considered as a first step to help in the development for more effective anti-HIV drugs and possible novel intervention therapy in the future. Present review article provides comprehensive insights on the above issue. We performed a comprehensive literature search in the bibliographic database "Pubmed," looking at studies discussing the SAMHDI and Vpx interactions.

Contents

1. Introduction

SAMHD1 (Sterile Alpha Motif and HD domain 1) is Human Immunodeficiency Virus (HIV) restriction factor in non-dividing

monocytes, dendritic cells (DCs), macrophages, and resting CD4+ T-cells. SAMHD1 hydrolyzes dNTPs and restricts HIV1 infection in macrophages and resting CD4+ T-cells by decreasing the intracellular dNTP pool. SAMHD1 is expressed at high levels in hematopoietic stem and progenitor cells (HSPCs) cultured in a medium enriched with cytokines. The intracellular dNTP pool in Dendritic Cells (DC) and its regulation by SAMHD1 is a common mechanism of HIV1 restriction in myeloid cells (Li et al., 2015, St. Gelais et al., 2012). SAMHD1 affects the Aicardi Goutieres syndrome (AGS) pathogenesis and can work as a major regulator of cellular dNTP levels in human cells and is also considered as the most sensitive activator for dNTP degradation (Ji et al., 2013).

The latest reports by World Health Organization (WHO) and the joint United Nations Program on HIV/AIDS (UNAIDS), indicates that up to 39.8 million (34 000 000–39 800 000) people acquired HIV infection by the end of 2015 (UNAIDS, 2016). In Saudi Arabia HIV was found in the blood donor and hemophilic patients. (Ramia et al., 1989). Number of HIV cases reported from Saudi Arabia, MOH, 1984 till 2015 accounted for 22,952 cases which includes 6770 Saudis and the remaining 16,182 Non-Saudis (MOH, Nov 30, 2016).

HIV infects T Cells, which leads to reduced adaptive immune response and an immunocompromised state develops. There are several general mechanisms by which HIV infection can cause alterations in cell numbers and in cell function. Finally, coinfection by a second pathogen can contribute to a breakdown in the host defense cascade leading to opportunistic infections. (Beck, 2005). The innate immune system plays an important role in the viral pathogen. Myeloid cells; such as monocytes, dendritic cells and macrophages have a multifaceted role in HIV initial infection and viral dissemination (St. Gelais and Wu, 2011). Recently, HIV2 has been shown to escape the host immune system by targeting a myeloid cell specific restriction factor, SAMHD1 (Hrecka et al., 2011) (Laguette and Benkirane, 2012) (Delucia et al., 2013).

2. SAMHD1

This newly discovered protein is shown to be expressed in non-permissive cells, primary monocytes, monocyte derived macrophages and dendritic cells. Recent studies have uncovered SAMHD1 as the restriction factor that blocks HIV1 replication in myeloid cells. It cannot block HIV2 replication due to the expression of VPX protein, which works by blocking SAMHD1 action. The restriction activity of SAMHD1 works by keeping intracellular levels of nucleotides low creating a poor environment for viral-DNA synthesis (Laguette and Benkirane, 2012).

Fig. 1 SAMHD1 comprises of two structural domains: a sterile α motif (SAM) domain and a dNTP triphosphohydrolyase (dNTPase) domain, which encompasses a metal-dependent phosphohydrolase homologous region with a conserved histidine and aspartate (HD) motif. These two domains are connected by a short linker and flanked by unstructured regions. The N terminus, preceding the SAM domain, contains a nuclear localization signal. The crystal structure of the dNTPase domain has been determined (Goldstone et al., 2011). They suggested that HIV1 replication is restricted by SAMHD1. C terminus is required for efficient depletion of dNTP pools and inhibition of HIV1 infection in monocytes (Yan et al., 2013).

It is expected that by studying the mechanisms underlying SAMHD1mediated HIV restriction will shed light on the innate immune response against retroviruses and assist in the future development of more effective anti-HIV interventions. The innate immune response of type 1 Interferon (IFN) in acute and chronic HIV1 infection is well identified together with plasmacytoid dendritic cells. IFN can also inhibit HIV1 in macrophages and play a role in immune-pathogenesis of the disease and the control of the invading viruses but the mechanism of IFN and HIV infection is not well known and needs further studies (Hughes et al., 2013).

2.1. The relationship of HIV2 and SAMHD1 in the immune response

Recognition of HIV2 infection is clinically important because it still causes significant morbidity and mortality worldwide. HIV-2 infections have been characterized by broad, low-magnitude intra type neutralization responses in several studies. Specific antibodies neutralized the virus and indicated that the viral envelope is highly immunogenic. In natural infection and high titre neutralizing antibodies are excreted, indicating that HIV2 is associated with delayed disease progression in many patients (Kong et al., 2012). HIV2 and SIV strain have the Vpx protein, but this protein is not encoded by HIV1 (Fig. 2) (Baldouf et al., 2012).

SAMHD1, an intracellular exonuclease prevents HIV replication by hydrolyzing deoxynucleoside triphosphates to inhibit reverse transcription of viral RNA. The effect of SAMHD1 on HIV1 strains is therefore to restrict their replication in dendritic and myeloid cells. Paradoxically, this might have been thought to enhance the relative pathogenicity of HIV2. One possible explanation for this counter-intuitive effect is that infection of dendritic cells triggers a type-1 IFN response, which is protective for the host. (Schaller et al., 2012, Lahouassa et al., 2012).

HIV2 is less pathogenic for humans than HIV1, and both viruses replicate in the T cells, only HIV2 replicates efficiently in dendritic cells (DCs) and activates innate immune pathways. (Xavier et al., 2013).

The SAMHD1 gene is located on chromosome 20 between the short (p) arm at the end (terminus) of the arm and the long (q) arm. SAMDH1 which has SAM and HD domain consist of 626-aminoacids protein. HD domain has hydrolase activity. Both Vpr and Vpx are involved in nuclear import. This indicates that Vpr lack the ability to counteract SAMHD1 restriction. This immune modulator SAMHD1 operating as a restriction factor in DCs might show new ways in vaccine strategy in DC (Lagutte et al., 2012).

SAMHD1 is responsible for blocking HIV1 replication within non-permissive cells. This indicates that there is an inverse relation between SAMHD1 expression and permissiveness to HIV infection. Moreover, disability of SAMHD1 in permissive cells leads to an increase in the HIV infection (Badia et al., 2017). SAMHD1 not only restricts the dNTPase activity but also the RNase activity (Beloglazova et al., 2013).

3. Expression of SAMHDI

SAMHD1 is expressed at high levels in (HSPCs) cultured in a medium enriched with cytokines (Li et al., 2015). Silencing of SAMHD1 markedly increases the susceptibility of monocyte-derived dendritic cells to infection (Wellbourn et al., 2013, Puig-domenech et al., 2013).

Human SAMHD1 possesses dual enzymatic functions. It acts as both a dGTP-dependent triphosphohydrolase and as an exoribonuclease. The dNTPase function depletes the cellular dNTP pool (Lahouassa et al., 2012). Another study by choi et al. showed that SAMHD1 directly targets HIV1 genomic RNA via its RNase activity, and this function is sufficient for HIV1 restriction. The dual function of SAMHD1 as dNTPase and RNse has a role in the HIV inhibition but it is not clear that how the activity of SAMHD1 is restricted to retroviruses. (Choi et al., 2015).
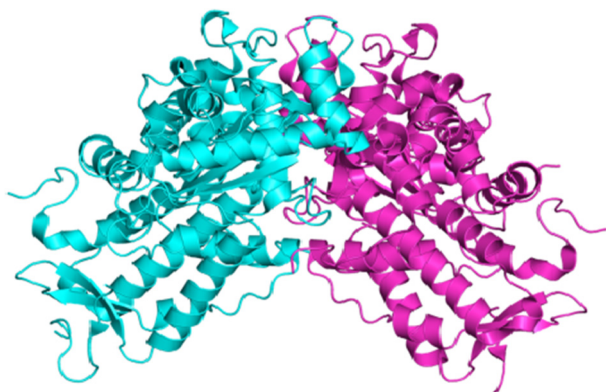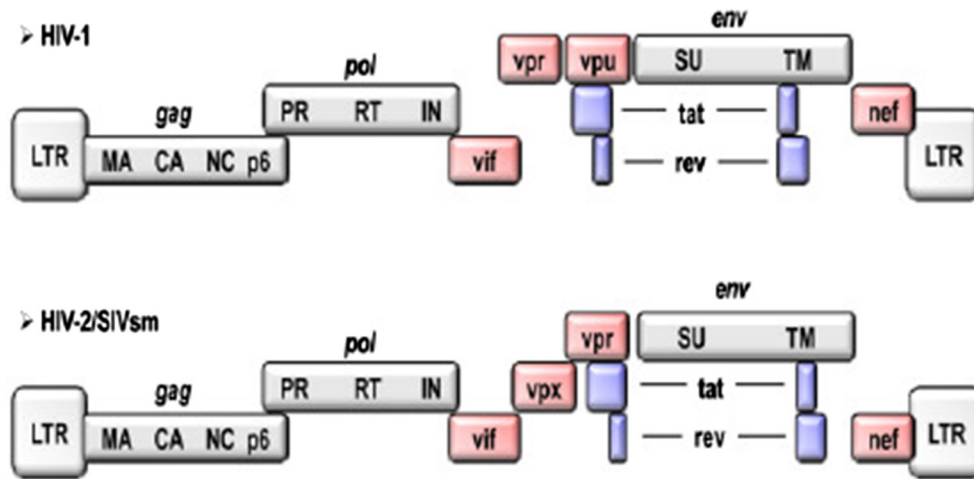

Fig. 1. Structure of the human SAMHD1.

Fig. 2. Schematic representation of HIV1 and HIV2 genomes. Grey boxes represent structural genes; blue boxes indicate regulatory genes; and pink boxes indicate accessory genes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.) *Source:* D Ayinde et al. Retrovirology 2010.
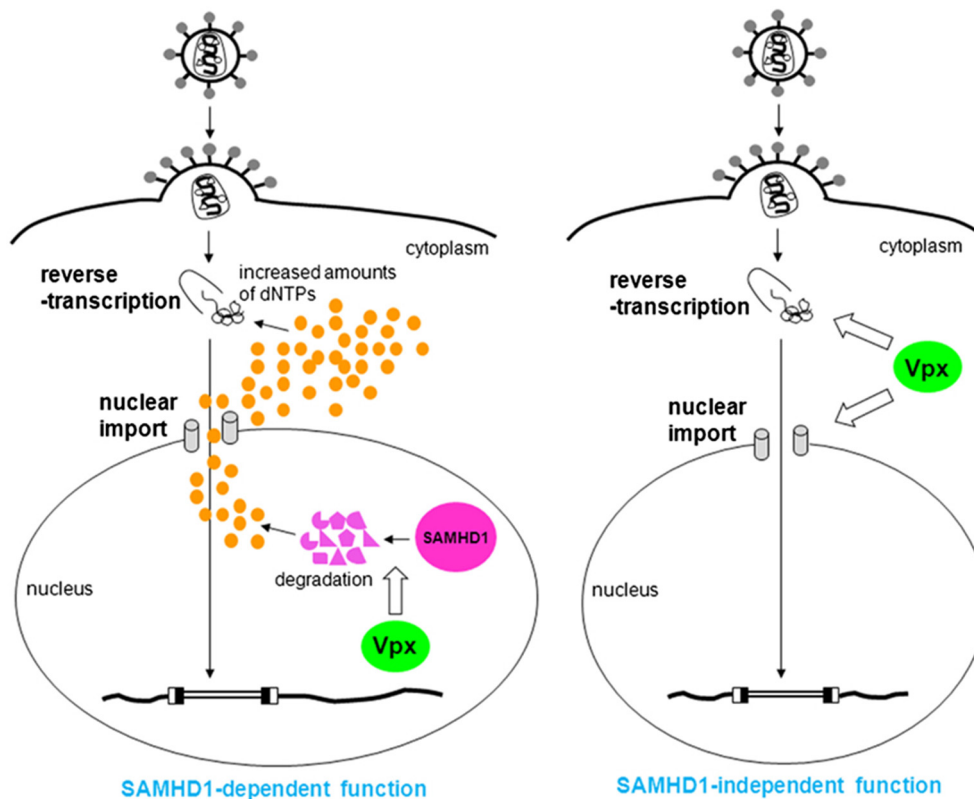
Fig. 3. SAMHD1-dependent and -independent functions of Vpx.. *Source:* www frontiersin.org

Fig. 3 SAMHD1 proteins are potent inhibitors of viruses, including retroviruses such as HIV1, HIV2, and SIV. Vpx, a distinctive viral protein expressed by HIV2 and some SIVs, induces SAMHD1 degradation (Buchanan et al., 2016). Restriction of HIV1 in myeloid-lineage cells is attributed in part to the nucleotidase activity of the SAM-domain and HD-domain containing protein (SAMHD1), which depletes free nucleotides, blocking reverse transcription (Antonucci et al., 2016).

Fig. 4 Unlike activated CD4$^+$ T cells, resting CD4$^+$ T cells are highly resistant to productive HIV1 infection because SAMHD1 is abundantly expressed in resting CD4$^+$ T cells. SAMHD1 imposes an effective restriction to HIV1 infection in the large pool of noncycling CD4$^+$ T cells (Baldouf et al., 2012).

Dendritic cells (DCs) whose functions are dependent on their degree of differentiation interfere with HIV1 replication due to the expression of SAMHD1 as restriction factor. In immature cells, productive HIV-1 infection activates IFN-related-genes involved in the control of viral replication thus inducing an antiviral state in surrounding cells. Paradoxically restriction of HIV1 by SAMHD1 would result in lack of sensing and IFN activation thus favoring initial HIV1 escape from innate immune response (Calonge, 2017).
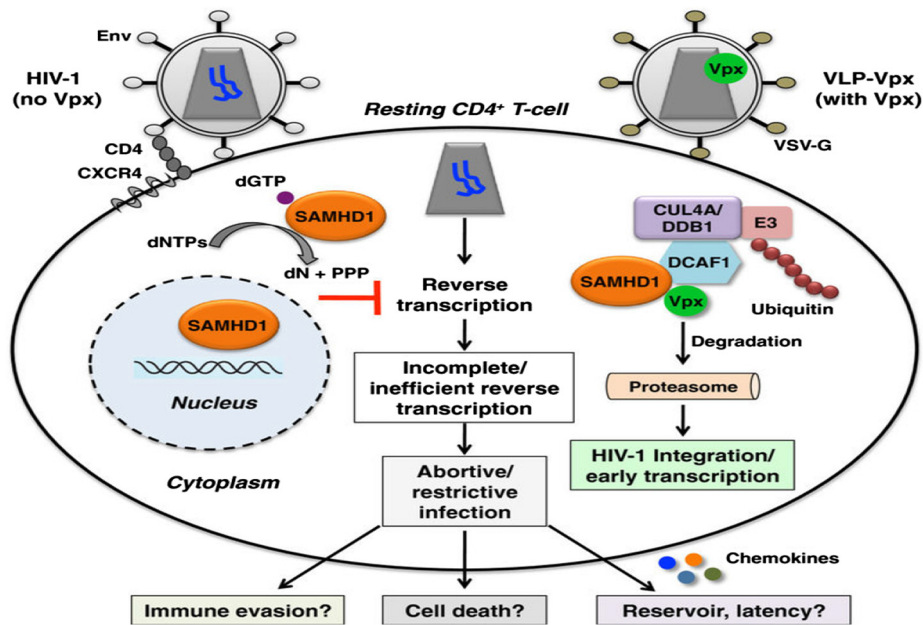
Fig. 4. SAMHD1 restricts HIV-1 infection in resting CD4^{+} T-cells. *Source:* Li Wu: Retrovirology, 2012: 9, 4690–4698)

Mediating restriction of HIV1 infection in quiescent T cells is the result of SAMHD1 role due to a block at reverse transcription. Importantly, CD4[±] T-cells from patients with Aicardi-Goutières Syndrome harboring mutation in the SAMHD1 gene display an increased susceptibility to HIV1 infection that is not further enhanced by VLP-Vpx-treatment. (Descours et al., 2012).

The Vpx protein from HIV2 or SIV antagonizes the effect of SAMHD1 by triggering its degradation. SAMHD1 significantly inhibits productive cell-to-cell transmission to target MDDCs and prevents the type I interferon response. Thus SAMHD1 can control both HIV1 and replication of host immune response (Puig-domenech et al., 2013).

4. Effect of SAMHDI against HIV

Ryoo et al., 2014 in their study found also that SAMHD1 restricts HIV-1 infection through its ribonuclease (RNase) activity by cleaving the viral RNA genome. The RNase activity of SAMHD1, but not its dNTPase activity, is essential for HIV-1 restriction in non-dividing cells.

SAMHD1 is a cellular dNTPase that restricts lentiviral infection presumably by lowering cellular dNTP levels to below a critical threshold required for reverse transcription and the exonuclease activity of SAMHD1 was reported to contribute to virus restriction (Welbourn et al., 2013). Antonucci et al. (2016) suggested that SAMHD1 does not have broad nuclease activity but did not rule out the interaction of SAMHD1 and HIV-RNA. Their results indicated the dNTPase activity of SAMHD1 acts as a primary antiviral mechanism. This is in contrast to Ryoo et al., who indicated that RNAse restrict HIV and this is could be due to the use of different SAMHD1 mutants. The result discrepancy might be due to different laboratory procedure, vector or reagents used (Antonucci et al., 2016).

White et al. in (2013) reported that HD domain of SAMHD1 is essential for the ability of SAMHD1 to oligomerize . They used purified SAMHD1 proteins from insect cells and demonstrated a direct interaction of SAMHD1 with RNA. They showed that enzymatic activity of SAMHD1 in cells can be inhibited by double-stranded RNA proposing the likelihood that RNA from a pathogen might modulate activity of SAMHD1. They showed that

SAMHD1 proteins, SAM and HD can restrict retrovirus and have the ability to block HIV1 infection and added that HD domain is sufficient to cause restriction of HIV1 and SIV.

5. Vpx protein countracts SAMHDI

Several authors reported that SAMHD1 restriction is counteracted by Vpx, which is encoded by HIV2 and SIV. Vpx binds DCAF1 DDB1- and CUL4-associated factor 1, a substrate receptor for the CRL4 (Cullin4 RING ubiquitin ligase) E3 ubiquitin ligase, and recruits SAMHD1 to the E3 ligase for proteasome-dependent degradation (Berger et al., 2011; Hrecka et al., 2011; Jauregui et al., 2015). Vpx facilitates transduction of dendritic cells and macrophages and relieves the inhibition of HIV-1 infection in restricting cells (Yu et al., 1991; Goujon et al., 2007).

Vpx has been demonstrated to load SAMHD1 to the CRL4 E3 ubiquitin ligase for proteosomal degradation by binding DCAF1, a substrate receptor of the ligase for proteosomal degradation. However, the precise molecular mechanism of SAMHD1 activation and the interplay between Vpx and host cellular factors, with respect to SAMHD1 down-regulation, are yet to be defined. (Delucia et al., 2013). SAMHD1, down-regulates dNTP pools in terminally differentiated and quiescent cells, thereby inhibiting HIV1 infection at the reverse transcription step. HIV2 and SIV counteract this restriction via a virion-associated virulence accessory factor, Vpx (Vpr in some SIVs), which loads SAMHD1 onto CRL4-DCAF1 E3 ubiquitin ligase for poly-ubiquitination, programming it for proteasome-dependent degradation (Descours et al., 2012).

It has been reported that the Vpx gene of HIV2 has different functions which is degradation of SAMHD1 in macrophages. The proline 109 exist in C- Terminal poly –protein motif of HIV2-Vpx regulates SAMHD1 degradation when there is high amount of Vpx. The genomes of HIV and SIV are complex and contain several accessory genes which modulate viral replication and pathogenicity. One of these genes, Vpx, is unique to the HIV2 group of viruses and encodes a virion-associated protein. Vpx is required for the production of fully infectious and cytopathic HIV-2 virions by facilitating viral entry and/or reverse transcription (Ciftci et al., 2015). The pronounced replicative defect of Vpx-deficient HIV2 in primary PBMCs is greatly observed but not in short-term cultures of

immortalized T-cell lines emphasizes the need to characterize the properties of nonessential HIV accessory gene products in natural target cells of unknown function (Kappes et al., 1991).

The mechanism by which SAMHD1 blocks viral infection, however, is controversially discussed, SAMHD1 as mentioned previously acts as a dNTP tri-phospho-hydrolase that cleaves dNTPs into nucleosides and inorganic triphosphates (Powell et al., 2011; Lahouassa et al., 2012). Alternatively, some reports describe nucleic acid binding and a nuclease activity of SAMHD1 (Belaglazova et al., 2013; Seamon et al., 2015).

It has been shown that phosphorylation of human SAMHD1 at threonine 592 (T592) by the cell cycle-dependent kinases 1 and 2 (CDK1 and CDK2) regulates the antiviral activity (Cribier et al., 2013; St. Gelais et al., 2014). However, recent work by three different groups showed independently that the phosphorylation of SAMHD1 at T592 down regulates the dNTP hydrolase activity of the protein, especially at low nucleotide concentration. This shows that SAMHD1 phosphorylate the antiviral activity (Arnold et al., 2015; Yan et al., 2015). These findings strongly suggest that the depletion of dNTPs by human SAMHD1 is the most likely mechanism of retroviral restriction.

SAMHD1 significantly increase the antiviral immune response, mediates the interferon-induced inflammatory response involved in the host foreign-virus defense system. In addition, SAMHD1 has been found to have $3' \rightarrow 5'$ exonuclease activity on single-stranded DNA and RNA, and these activities may play a role in restriction by degrading the viral genomic RNA (Belaglazova et al., 2013).

5.1. Discussion

Lower transmission, low viral loads and reduced progression to AIDS are characteristics of HIV2 infection. HIV1 is characterized by high transmission, high viral loads and it leads to AIDS faster than HIV2. In Saudi Arabia, the number of HIV2 is rare. Only 5 cases of HIV2 have been seen in KFSH&RC (Almaghribi et al., 2011). Harris et al., 2012 emphasized that although HIVI has Vpr protein but does not inhibit SAMHD1 as the virus has no Vpx. This might lead to the resistance situation of myeloid cell to HIV1 infection and the low pathogenicity of HIV2 than HIV1. Better immunity response could be produced by small- molecule inhibitors of SAMHD1 (Harris et al., 2012).

In 2011, there were two studies that first investigated the protein interaction between Vpx and SAMHD-1. They confirm that Vpx interacts with SAMHD1 and induces proteasomal degradation of SAMHD1 in macrophages. The first group was of Laguette et al. identified SAMHD1 protein interacting with Vpx when they infected with HIV1. Later, they added a virus like particles that has Vpx (VLP-Vpx) derived from SIVmac to the cells. They showed that Vpx induces proteasomal degradation of SAMHD1.

The other study by Hrecka et al. (2011) demonstrated that Vpx relieves the inhibition of HIV1 infection in monocyte-derived macrophages by mediating proteasome-dependent degradation of SAMHD1 through the CUL4A/DCAF1 E3 ubiquitin ligase and degradation of SAMHD1 by Vpx is initiated in the nucleus (Brandariz-Nuñez et al., 2012).

Fregoso et al., 2013 in their study of Vpx/Vpr results on restriction on SAMHD1, found that Vpx from HIV2 and SIV mac lineage, needs the C-terminus of SAMHD1 for interaction and degradation. They added that SAMHD1 is counteracted by Vpx and Vpr and this is due to the recognition of several interfaces of SAMHD1 by both Vpx and Vpr, and this data illustrate a novel phenomenon for recognizing the restriction factor and the viral antagonist.

Fujita et al., 2012 reported that the 2 genes Vpx and Vpr exist in HIV 2 while HIV 1 encodes only Vpr gene. The Vpx mediates the degradation of SAMHD1, which counteract host defense

mechanisms, enabling reverse transcription to act in low dNTP concentration. The SAMHD1 dependent and independent function are controlled by different regions of the Vpx protein. Vpr protein of HIV1 can play different functions. They indicated that HIV1-Vpr affects viral replication and enhances nuclear import of the viral gene. The HIV2-Vpx could enhance nuclear import. Further studies are needed to evaluate the role of Vpx and Vpr in SAMHD1.

Lim et al., 2012 explained that Lentivirus restriction in DC and monocyte/macrophages is carried out by SAMHD1, and this is antagonized by Vpx gene of HIV2 which cause degradation of SAMHD1. This Vpx is encoded by 2 of 8 primate lentivirus, where as Vpr gene exist in all lentivirus. Therefore, SAMHD1 degdration depends on binding sensitivity of Vpx and concluded that SAMHD1 were noticed by Vpr prior to Vpx.

In 2017 Ordoniz et al. reported that different antiviral drugs such as acyclovir and gancyclovir which inhibits herpes viruses and the anti-cancer drugs cloferabine are considered as anti – HIV1 agents in case of low dNTPs. These suggest novel uses as nucleotide analogues for HIV1inhibition.

6. Conclusion

SAMHD1 is a cellular enzyme responsible for blocking HIV replication in myeloid cells. SAMHD1 converts deoxynucleotide triphosphates to inorganic phosphates and deoxynucleosides, thus depleting the nucleotide pool and preventing HIV1 reverse transcription to synthesize viral cDNA. Viral accessory protein (Vpx) in HIV2 plays an important role in suppressing the antiviral protein SAMHD1 in myeloid cells by proteosomal degradation. Both Vpr and Vpx has high sequence homology and are involved in nuclear transport, but Vpx is more powerful in the disruption of viral replication. SAMHD1 inhibits cell to cell transmission and prevent type 1 IFN response. It restricts not only dNTPase activity but also the RNase activity. Silencing SAMHD1 enhances HIV I infection of myeloid cells and resting CD4T cells.

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