GLOBAL JOURNAL OF BIO-SCIENCE AND BIOTECHNOLOGY

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SAMHD1 AND HIV1 INFECTION: A NEW APPROACH

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ABSTRACT
Sterile alpha motif and histidine aspertate domain containing protein 1(SAMHD1) is a new hope for the treatment of AIDS. Millions of people are suffering from AIDS since there is no definite treatment available for this life threatening disease at present. Moreover several hurdles are associated with the treatment procedure. Several strategies have been developed to counteract this syndrome, out of which HAART is the best one. This antiretroviral therapy represses the viral growth rate hence prolongs the patient's life. However it cannot fully cure the infection, thus it is necessary to develop such strategy which can fully cure this life threatening infection. Some components have been identified in the different researches as the potential anti HIV agents, among which we observed SAMHD1 has an effective antiretroviral activity. So, in this review, we have tried to characterize the SAMHD1 and have also discussed about the approaches that can be used for the treatment with SAMHD1. Research development of treatment procedure with SAMHD1 can open up a new era which can save million of life suffering from AIDS.

KEYWORDS: SAMHD1, AIDS, HAART, HIV.

INTRODUCTION:
Human immunodeficiency virus (HIV) was identified as a human infectious pathogen in 1958. It is a retrovirus and it generally infects $CD4^+$ T cells [Barré-Sinoussi *et al*., 1983, Laguette *et al*., 2012]. Eventually the infection leads to chronic activation of immune system, functional impairment and consequent loss of $CD4^+$ cells [Hazenberg *et al*., 2003, Fu *et al*., 2016]. At present, near about 30 million people are being infected with the virus and consequently 2 million people becomes infected per year worldwide [Hertoghs *et al*., 2015]. AIDS is a state of pathological alteration in humans where weakness in immune response [Che *et al*., 2010] allows life threatening opportunistic infections and cancers to occur. Activation of $CD4^+$ T cells can be impelled by non-replicating HIV1 and it can also cause excessive $CD4^+$ T cells depletion by cell lysis and apoptosis [Doitsh *et al*., 2013, Holm *et al*., 2005]. Although these activated $CD4^+$ T cells are extremely permissive to HIV-1 infection but the resting/quiescent $CD4^+$T cells are turbulent to HIV-1 infection [Zack *et al*. 1990, Eisele *et al*. 2012, Gao *et al*. 1993, Wu 2012, Baldauf *et al*. 2012].
Sterile alpha motif and histidine-aspartic domain containing protein 1 (SAMHD1) is a cellular enzyme that inhibits the ability of retroviruses specifically HIV-1 to infect myeloid cells, non cycling cell types which includes monocytes, dendritic cells, macrophages and resting $CD4^+$ T cells [Goldstone *et al*. 2011, Powell *et al*. 2011, Wang *et al*. 2014, Berger *et al*. 2011, Dragin *et al*. 2013, Puigdomènech *et al*. 2013, St. Gelais *et al*. 2012, Descours *et al*. 2012]. SAMHD1 was discovered in the year 2000 as a component of human innate immune system and named dendritic cell derived IFN-gamma induced protein (DCIP) [Li *et al*. 2000]. In most human organs specifically in skeletal muscles and heart, DCIP mRNA is expressed constitutively [Franzolin *et al*. 2013]. Researchers have showed that sequences of distantly related genes were found in broad spectra of eubacteria and archea and from humans to nematodes in case of eukaryotes. DCIP was later renamed SAMHD1 when its structure containing two previously known protein modules were identified [Laguette *et al*. 2011]. SAMHD1 comprises of three regions: N terminal short SAM (sterile alpha) domain (residues 1-109), a deoxyribonucleoside triphosphate triphosphohydrolase (dNTPase) catalytic core domain (residues 110-599) and a C terminal longer HD domain with a conserved doublet of histidine and aspartate (residues 600-626) [Ahn *et al*. 2016, Qiao *et al*., 2005, Aravind *et al*. 1998]. SAMHD1 containing SAM domain is a putative protein-protein and protein-nucleic acid interaction module and the C terminal HD domain is found in diverse families of phosphohydrolases [Powell *et al*., 2011]. HD domain has greater importance over SAM domain in that it can show full catalytic activity in the absence of SAM domain [Aravind *et al*., 1998]. Over expression of the HD\AA. AA 206-207 mutant SAMHD1 in U937 cells are not able to restrict HIV-1, which suggests that the phosphodiesterase activity of the HD domain is necessary for the inhibition of infection by SAMHD1. Further analysis discovered that the HD domain of SAMHD1 is responsible for its dGTP stimulated dNTPase activity [Laguette *et al*., 2011, Goldstone *et al*., 2011, Powell *et al*., 2011] . The amino acid sequences of SAMHD1 considered this protein as metal dependent phosphohydrolase [Powell *et al*., 2011]. Several biochemical studies have characterized SAMHD1 dNTPase activity and revealed that inactive SAMHD1 exists in monomer or dimer form which undergoes tetramerization to generate it's catalytically active form [Yan *et al*., 2013] and the stability of this tetramer is related to the HIV-1 restriction activity of SAMHD1.The C terminus located outside the catalytic core domain confers stability and after identification of the core domain independently by two groups, the structural basis for dGTP induced SAMHD1 tetramerization was revealed [Ji *et al*., 2013, Zhu *et al*., 2013]. Several proteins called restriction factors are identified in the cells which arrest the replication cycles of SAMHD1 such as–TRIM 5 alpha, APOBEC3G, Tethrin or BST-2 [Sheehy *et al*., 2002, Stremlau *et al*., 2004, Neil *et al*., 2008]. Tripartite motif (TRIM) 5 alpha: It interferes with the uncoating step by binding to the viral capsid (CA) and then disorders the lattice [Laguette *et al*., 2012]. But human TRIM 5 alpha harbors amino acid substitution which abrogates its restriction potential [Yap *et al*., 2005]. Apolipoprotein B mRNA-editing enzyme catalytic polypeptide link 3G (APOBEC3G / A3G): It is a type of cytidine deaminase which disrupts the early steps of viral life cycle [Stopak *et al*., 2003, Mariani *et al*., 2003]. Vif binds with A3G and degrades it polyubiquitination and proteasome in infected cells thus prevents the entry of it into nascent viral particles [Yu *et al*., 2003]. Also HIV counteract to A3G in Vif independent manner [Dang *et al*.,

2008]. Bone marrow stromal cell antigen 2 (BST-2) / Tethrin: It tethers nascent viral particles into the plasma membrane thus prevents their release and reinfection of new target cells [Neil *et al*., 2008]. Another viral auxillary protein Vpu interacts with BST-2 and sequesters it away from its site of action and in the absence of Vpu, other viral proteins inhibits it [Kirchhoff, 2009]. SAMHD1 is of great importance in contrast to previously recognized HIV-1 restriction factors due to the fact that SAMHD1 does not meet a counterattack developed by HIV-1 [Cribier *et al*., 2013]. The enzyme reverse transcriptase of HIV1 with low Km binds to dNTPs with high affinity [Diamond *et al*., 2004] which confers lower levels of reverse transcription in non-cycling cells [Ayinde *et al*., 2012, Lahouassa *et al*., 2012, Kim *et al*., 2012, Amie *et al*., 2013] whereas reverse transcriptase of HIV2 has lower affinity to dNTPs [Fujita *et al*., 2012]. It is a deoxynucleoside triphosphate phosphohydrolase which cleaves deoxynucleoside triphosphates (dNTP) into deoxynucleosides (dN) and inorganic triphosphates (iPPP) [Powell *et al*., 2011, Goldstone *et al*., 2011, Kim *et al*., 2012, White *et al*., 2013, Hrecka *et al*., 2011, Amie *et al*., 2013, Beloglazova *et al*., 2013] as well as lowers the concentration of dNTPs below the level required for reverse transcription of HIV1 [Lahouassa *et al*., 2012, Franzolin *et al*., 2013, Schaller *et al*., 2012]. Inhibition of reverse transcription prevents the synthesis of full length double stranded DNA and also disorders later stages of the viral life cycle which includes nuclear translocation and integration of proviral DNA [Baldauf *et al*., 2012, Goujon *et al*., 2013]. Restriction function of SAMHD1 has been recognized in non-cycling cells such as monocytes [Berger *et al*., 2011], macrophages [Dragin *et al*., 2013], dendritic cells [Puigdomènech *et al*., 2013, St. Gelais *et al*., 2012] and resting $CD4^+$ T cells [Descours *et al*., 2012].

MECHANISM OF HIV-1 RESTRICTION:

Limiting reverse transcription by dNTPase:

SAMHD1 is usually accepted as a host restriction factor for HIV1 infection which controls dNTP pools in immune cells. It cleaves deoxynucleoside triphosphates at the alpha-phosphate position which generates inorganic triphosphates and deoxynucleosides , thus depleting dNTP pool which is required by cellular DNA polymerase [Baldauf *et al*., 2012, Goldstone *et al*., 2011]. So the early steps of reverse transcription are blocked due to low levels of dNTPs in resting cells. HIV1 can initiate reverse transcription but cannot complete the full length HIV1 cDNA synthesis, SAMHD1 can inhibit the synthesis of full length double stranded DNA, impede later stages of viral life cycle which includes nuclear translocation , integration of proviral DNA and gap repair during HIV1 integration [Zack *et al*., 1990, Gao *et al*., 1993, Diamond *et al*., 2004, Lahouassa *et al*., 2012]. The overall mechanism is discussed in figure1.

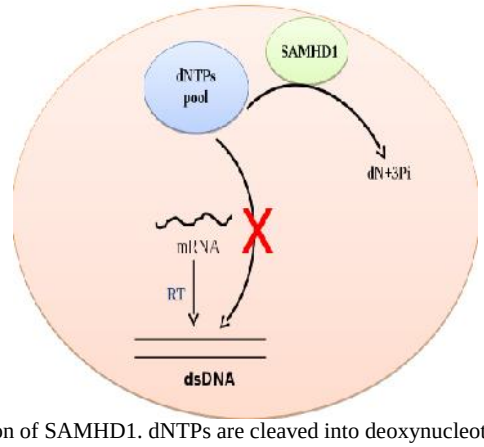

FIGURE 1: General mechanism of action of SAMHD1. dNTPs are cleaved into deoxynucleotides (dN) and inorganic phosphates (P_i). Due to lack of dNTPs, reverse transcription (RT) is inhibited.

Structure of SAMHD1 helps in restriction:

Tetramerization of SAMHD1 is required for its biological activity and efficient restriction of HIV-1 infection and the intracellular localization of SAMHD1 protein has no role in inhibition of infection [Brandariz-Nuñez *et al*. 2012, Hofmann *et al*. 2012]. Earlier it was identified that N terminus truncated protein of SAMHD1 is dimeric [1Goldstone *et al*. 2011] but by using a combination of biochemical and virologic approaches they identified the functional organization of SAMHD1 and its tetrameric state in monocytic cells which strongly restricts HIV-1 infection in contrast to its dimeric form [Yan *et al*. 2013]. Also the oligomerization of SAMHD1 is not efficient in restriction activity [White *et al*. 2013, Brandariz-Nuñez *et al*. 2012]. Chemical cross-linking studies showed that the tetrameric form is regulated by its C terminus which is essential for its full activity to deplete dNTP pool as well as to inhibit HIV1 infection. Also C terminus of SAMHD1 protein has a docking site for Vpx protein which degrades SAMHD1 by proteasomal degradation and the C terminus mostly divergent in SAMHD1 proteins from different primates and vertebrate species [Laguette *et al*. 2012, Ahn *et al*. 2012]. Variable C terminal domain and conserved SAM domain is present in vertebrate SAMHD1 proteins which indicates its importance in cellular function. Deletion of N terminal region and SAM domain of SAMHD1 mislocalizes it into cytoplasm which confers no change in its restriction activity. The dNTPase activity of SAMHD1 is induced by deoxyguanosine triphosphate (dGTP) binding at a predicted allosteric sites of HD domain [Goldstone *et al*. 2011, Powell *et al*. 2011]. Also HD domain is required for the activity of SAMHD1 in restriction of infection in non-dividing cells [Laguette *et al*. 2011]. The other domains of SAMHD1 are not well established.

Nuclease activity of SAMHD1:

Besides the dNTPase activity of SAMHD1, metal dependent 3'-5' exonuclease activity also may contribute to HIV1 infection restriction by binding and degrading retroviral genomic RNA or transcribed viral mRNA, and also cDNA products from reverse transcription [Beloglazova *et al*., 2013, Goncalves *et al*., 2012, Tüngler *et al*., 2013]. It was found that SAMHD1 is a nucleic acid binding protein preferably with RNA over DNA. The fluorescence cross-correlation spectroscopy reveals that SAMHD1 specifically binds with single stranded RNA and DNA and the nucleic acid binding and SAMHD1 complex formation are correlated with each other. The

interaction between nucleic acid and SAMHD1 complex formation requires HD domain and C terminal region of SAMHD1 but not the SAM domain. This phenomenon established by the mutations linked with Aicardi-Goutieres syndrome (AGS), showed both impaired nucleic acid binding and SAMHD1 complex formation. These results suggests the role of SAMHD1 in nucleic acid metabolism , linked with cell proliferation and cell cycle regulation. SAMHD1 specifically breaks 3' overhangs of double stranded DNA/RNA substrates and RNA in blunt ended DNA/RNA duplexes.

REGULATION

Phosphorylation mediated regulation:

SAMHD1 expression can be regulated by phosphorylation which is a post-translational modification [Herold *et al*., 2017]. SAMHD1 is simultaneously expressed in both cycling and non-cycling cells but it can inhibit HIV1 infection only in non-cycling cells [Baldauf *et al*., 2012, Descours *et al*., 2012]. In contrast to non-cycling cells, the SAMHD1 is phosphorylated in cycling cells at the position 592 of threonine (T592), which is mediated by cyclin dependent kinase CDK1/2 [Cribier *et al*., 2013, White *et al*., 2013, Ballana *et al*., 2014, Tang *et al*., 2015, Ruiz *et al*., 2015]. Human phosphor-proteome studies indicates phosphorylation at serine residues 33 and 93 [Bian *et al*. 2014, Zhou *et al*., 2013] and another study showed that the gross SAMHD1 phosphorylation is conferred by N-terminal phosphorylation [Badia *et al*., 2017].

Cell cycle dependent regulation

An enzyme, ribonucleotide reductase (RNR) is a key enzyme in de novo synthesis of dNTP in contrary to SAMHD1. It converts ribonucleoside diphosphates (NDPs) to deoxyribonucleoside diphosphates (dNDPs) which after subsequent phosphorylation converts into deoxyribonucleotides (dNTPs). SAMHD1 is downregulated while RNR is upregulated during the S-phase of the cell cycle mediating dNTP pool expansion for nuclear DNA synthesis [Aye *et al*., 2015]. SAMHD1 is highly expressed in G_0 and G_1 [Ballana *et al*., 2014].

Promoter methylation:

Lower expression of SAMHD1 may be associated with malignant diseases on mRNA and protein level [de Silva *et al*., 2013, de Silva *et al*., 2014]. Several studies suggested that lower expression is associated with promoter methylation and elevation or reduction of dNTP levels bear mutagenic potentials [Bester *et al*., 2011, Kunz *et al*., 1988, Chabosseau *et al*., 2011, Meuth *et al*., 1989, Wilkinson *et al*., 1989]. Later studies on lung cancer, revealed that mRNA level of SAMHD1 was much higher than the protein level, further suggested that post-transcriptional and or post-translational modification may occur.

There are also several other mechanisms by which SAMHD1 can be regulated. SAMHD1 can also be regulated by inhibiting the formation of SAMHD1 homotetramer by the binding of single stranded DNA and RNA species of 60 nucleotides to SAMHD1 dimers [Seamon *et al*., 2015]. Recently it has been reported that inhibition of SAMHD1 tetramerization and dNTPase activity is mediated by crosslinking cysteine residue 522 to either C341 or C350 in an oxidative intracellular environment [Mauney *et al*., 2017] and is further suggested by the fact that malignant tumours are usually exposed to higher levels of intracellular oxidative stress [Costa *et al*., 2014]. Histone acetylation may be also involved in regulation of SAMHD1 expression [Wang *et al*., 2014]. The H206 and D207 residues of HD domain play a crucial role in dNTPase activity of SAMHD1, whereas mutations to either H206 and D207 abroagates ssDNA binding as well as inhibits tetramer formation, which may suggest that SAMHD1 may regulate its dNTPase activity through NA binding [Ji *et al*., 2013, White *et al*., 2013, Beloglazova *et al*., 2013, Seamon *et al*., 2015]. Some studies show that SAMHD1 can be induced by IFN following IFN stimulatory DNA treatment [Rice *et al*., 2009] and also by a combination of IL-12 and IL-18 [Pauls *et al*. 2013].

APPLICATIONS:

The application of SAMHD1 as the antiretroviral medicine is a challenge for scientists. Though lots of treatment strategies are present to counteract the AIDS but it is true that no one strategy can cure the lethal syndrome fully. So research is going on the inhibition of AIDS. In these circumstances, we strongly believe that SAMHD1 has the potential to act as an antiretroviral agent which can inhibit HIV to some extent. To apply this agent, three approaches are hypothesized by us.

Approach 1:

Nucleoside reverse transcriptase inhibitors (NRTIs), which are agents lacking 3' OH moiety of ribose sugar ring that precisely retards HIV1 infection and is a key ingredient of highly active antiretroviral therapy (HAART) which maintains low viral load [Erb *et al*., 2000, Bangsberg *et al*., 2001]. It is administered as a nucleoside derivative which facilitates crossing of cellular membrane. After entering into the cell, host nucleoside and nucleotide kinases phosphorylates NRTIs and converts them into their triphosphate form. NRTI-TPs are used by viral RTs as a substrate over dNTPs. DNA chain elongation is inhibited after the incorporation of NRTI-TPs into proviral DNA due to the inhibition of formation of the phosphodiester bond with an incoming dNTP [De Clercq *et al*., 2009]. But NRTIs redundantly interacts with several host molecules such as DNA polymerase gamma, mitochondrial DNA polymerase etc leading to off-target effects [Feng *et al*. 2001, Feng *et al*., 2004, Lee *et al*., 2003]. It was identified that SAMHD1 influences the activity of NRTIs against HIV1 infection [Amie *et al*., 2013]. So, the combination of SAMHD1 and NRTI can efficiently fight against HIV1 infection. It is demonstrated in figure 2.

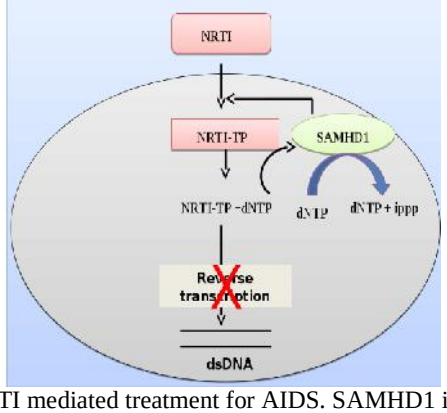

FIGURE 2: ***APPROACH 1:*** NRTI mediated treatment for AIDS. SAMHD1 influences the formation of NRTI triphosphate (NRTI-TP) which can mimic the role of dNTPs and inhibits reverse transcription of HIV.

Approach 2:

p53, a tumor suppressor gene, plays a key role in restriction of HIV1 infection. p53 can be induced by interferons Type 1 in human immune cells after HIV1 infection [Genini *et al*., 2001, Imbeault *et al*., 2009, Yoon *et al*., 2015, Takaoka *et al*., 2003] and the restriction employed by p53 can be done by various mechanisms such as – inhibition of LTR promoter, suppression of Tat by phosphorylation *etc* [Duan *et al*., 1994, Gualberto *et al*., 1995, Bargonetti *et al*., 1997, Li *et al*., 1995]. Recently, scientists suggested that p53 affects HIV1 reverse transcription [Bakhanashvili, 2001, Bakhanashvili *et al*., 2004]. Low level laser therapy (LLLT) can induce the expression of p53 at certain level required to inhibit the viral infection [Lugongolo *et al*., 2017]. Also the increased expression of p53 further induces the expression of its downstream gene p21. p21, a cyclin dependent kinase inhibitor, has an antiretroviral function by inhibiting CDK2 dependent phosphorylation of SAMHD1 [Ballana *et al*., 2014, Leng *et al*., 2014, Allouch *et al*., 2014]. Both the p53 and p21 combinely restricts HIV1 early stage replication [Shi *et al*., 2018]. It is demonstrated in figure 3.

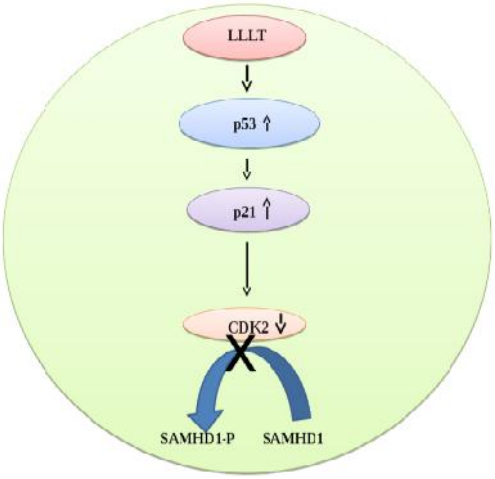

FIGURE 3: ***APPROACH 2:*** Low level laser therapy (LLLT) mediated treatment for AIDS. LLLT induced the expression of p53 which lead to the over expression of p21. These events lead to the down regulation of CDK2 that can reduce the phosphorylation of SAMHD1 (inactivation).

Approach 3:

IFNs are chemokines which activates innate immunity by enhancing the expression of Inter Stimulated Genes (ISGs). There are several types of ISGs that helps in antiretroviral restriction and one of them is Interferon Induced Transmembrane (IFITM) [Schoggins *et al*., 2011, Bailey *et al*., 2014, Narayana *et al*., 2015]. IFITMs are localized into the cell surface and it inhibits the entry of HIV1 into the host cell and it is also reported that it inhibits the activity of Vpx proteins which can efficiently degrade SAMHD1. Thus it can be hypothesized that IFITM treated cells are required to use SAMHD1 as the remedy for HIV2 infection [Roesch *et al*., 2018]. It is demonstrated in figure 4. But extensive study is required in this field.

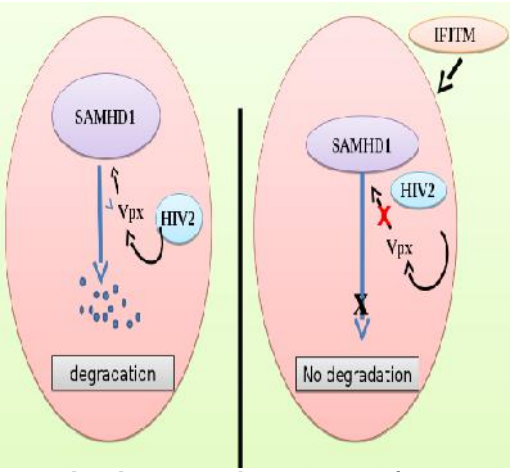

FIGURE 4: ***APPROACH 3:*** Interferon Induced Transmembrane (IFITM) for AIDS (especially for HIV2 treatment). VPX degrades SAMHD1 effeciently.VPX protein activity is inhibited by IFITM. So there is no reduction in the antiretroviral activity of SAMHD1.

CONCLUSION

Day by day, the rate of AIDS occurrence is increasing. So it has become very important to develop a new treatment strategy for AIDS. So, keeping the fact in mind, in this review we have focused on SAMHD1 as a viral restriction factor. SAMHD1 may open a new possible way to treat the HIV1 infection. SAMHD1 is a dNTPase, thus it blocks reverse transcription of HIV1 as dNTPs are key molecule in this mechanism. Here we have discussed some approaches for the application of SAMHD1 on restriction of HIV1 infection. This review work may prove to give encouragement and updated valuable information for characterizing SAMHD1 and use it as a remedy for AIDS.

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Abbreviation:

HIV: Human immunodeficiency virus; **SAMHD1:** Sterile alpha motif and histidine-aspartic domain containing protein 1; **dNTPase:** deoxyribonucleoside triphosphate triphospho hydrolase, **TRIM :**Tripartite motif; **APOBEC3G / A3G:** Apolipoprotein B mRNA-editing enzyme catalytic polypeptide link 3G; **dN:** deoxynucleosides; **iPPP:** inorganic triphosphates, **AGS:** Aicardi-Goutieres syndrome, **LLLT:** Low level laser therapy.