Saudi Pharmaceutical Journal 26 (2018) 903–908

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Review

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

Talal M. Bakir

Department of Clinical Laboratory Science, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

ARTICLE INFO

Article history:
Received 15 May 2017
Accepted 10 March 2018
Available online 12 March 2018

Keywords:
HIV-1
HIV-2
SAMHD1
Vpx protein
Macrophages

ABSTRACT

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).

E-mail address: tbakir@ksu.edu.sa
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2018.03.005

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).

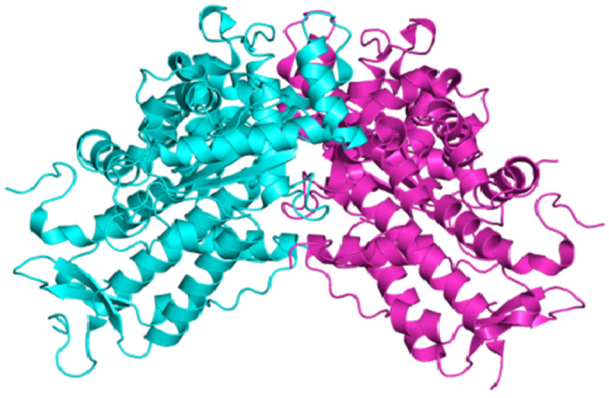

Fig. 1. Structure of the human SAMHD1.

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, Puigdomenech 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).