

MINI REVIEW

Epigenetics: Quest for no-escape to HIV, a persistent pathogen

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Abstract: Acquired Immune Deficiency Syndrome (AIDS) is a disease infection mix, which is primarily because of 'deficient' immune system. Human Immune-deficiency Virus (HIV) makes the immune system susceptible to many infections by infiltrating it. Many researchers believe that HIV is a mutated form of Simian Immune-deficiency Virus (SIV). After being clinically discovered in 1981 in America, it is said to have caused 36 million deaths. Treatment of AIDS has been a 'burning ' issue ever since its discovery. There is no cure for AIDS! Although, Recombinant Transcriptase Inhibitors (RTIs) are being considered a major treatment against HIV that can not only lessen the effect of HIV but also can prolong the life of HIV positive patients. More recent advancement includes 'transplantation of transgenic stem cells' in HIV positive patients. As latency of HIV provirus in host genome is the preeminent weapon of this virus against RTIs that compel it to hide from host immune system and a persistent pathogen thereof. Thus, epigenetic activation of latent provirus pool by methyl inhibitors along with nontoxic chemical drugs seems to be a more promising treatment to avoid the burden of lifelong RTI.

Keywords: Epigenetics, HIV, recombinant transcriptase inhibitors (RTI).

INTRODUCTION

History and introduction

There are different views and myths regarding the origin of HIV (Human Immune Deficiency Virus). Some researchers believe that origin of HIV-1 and HIV-2 lies in non-human primates, particularly chimpanzee and monkeys, in West-central Africa and were transferred to humans in the early 20th century (UNAIDS, 2007).

According to another school-of- thought, the people who acquired SIV were normally the hunters. After, several individual to individual transmissions of SIV (Simian Immune Deficiency Virus), its mutant form, HIV appeared. Some genetic studies about the virus suggest that the most recent common ancestor of the HIV-I M group, linking HIV epidemic to the increasing population of colonial African cities dates back to 1910. The spread of prostitution and unsafe sex also constitute the factors which do contribute. Another alternative view throws light on the unsafe medical practices and unsterile reuse of disposable syringes during mass vaccination in Africa after World War II, being the major vector of virus transmission (Sharp *et al.*, 2001; Kalish *et al.*, 2005). In 1981 in the USA, first time AIDS (Acquired Immune Deficiency Syndrome) was observed in the clinic. Initially, homosexuals and injectable drug users were

reported to have compromised immune system with symptoms of *Pneumocystis carinii* pneumonia (PCP) (Gottlieb, 2006).

Earlier, the CDC (Centre for Disease Control) could not coin any specific name for the disease and they referred to it by the diseases and symptoms associated with it, such as, lymphadenopathy and opportunistic infections. It was also named as "the 4H disease", in accordance with the type of people (Haitians, homosexuals, hemophiliacs and heroin addicts) it prevailed in. Finally, in 1982 the disease was referred as AIDS by CDC.

In 1983, research groups led by Robert Gallo and Luc Montagnier published their work in a journal, *Science*, independently declaring that a novel retrovirus may have been infected people with AIDS. Later, in 1986, this virus was renamed as 'HIV' (Barre -Sinoussi *et al.*, 1987).

AIDS (acquired immune deficiency syndrome) is not a disease itself. In fact, it is a combination of diseases which occur due to compromised immunity of human body. This syndrome is followed by infection with a retrovirus known as HIV (human immunodeficiency virus). The virus makes human body susceptible towards different infections and tumors, by interfering with human immune system, which otherwise won't have any major impact on human health (Gilbert *et al.*, 2007).

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The primary causes of HIV transmission can be unsafe oro-anal sex practice, blood (unscreened) transfusions, unsafe use of hypodermic needles and viral transmission during pregnancy or delivery from (mother to child). Earlier it was thought that different body fluids, for instance tears and saliva also transmit HIV, but researches on its modes of transmission excluded them from the list (MMWR Morbidity and Mortality Weekly Report, 1982).

HIV infection is something to prevent than to cure. A person can live 9-12 years without having proper treatment such as antiviral treatment. According to the statistical data published in 2012, almost 35.3 million people were said to be living as HIV positive. It is also stated that AIDS has been the cause of 36 million deaths worldwide, which undoubtedly makes it a pandemic (Kallings, 2008).

In this article, we have reviewed the advances in treatment and cures suggested to combat this deadly virus. But first will look at mechanism of HIV action and that how it attacks.

Mechanism of HIV

Our body is defended by white blood cells. HIV attacks these cells (lymphocytes) to destroy body defense system. The two glycoproteins gp120 and gp41 play key role in viral attachment and membrane fusion. CD4 is a cell surface receptor present on lymphocytes that become factory for viral particle production. HIV uses CD4 receptor along with co receptors in many cell types like T lymphocytes dendritic, natural killer cells and FC receptor in fibroblasts that lack CD4 receptor, to get entry into cell (Yu *et al.*, 2008). Once it gets entry into host cell being retroviral synthesizes its DNA and inserts into host genome followed by generation of innumerable copies.

When HIV enters in body, it is picked up by immune system's Antigen Presenting Cells (APC) that carries it to lymph nodes. HIV is transferred through process of *Transinfection* from APCs to Th cells. Th (T helper) cells present in lymph nodes are principal sites for HIV replication. It dictates Th cells to multiply and destroy immune system (Moris *et al.*, 2006).

Apoptosis results in the release of thousands of infectious virus particles to infect other cells (Gougeon, 2003).

It is believed that sexual practice is a major HIV transmission mode. Dendritic cells have a vital role in the initiation and persistence of viral infection in AIDS. Immature dendritic cells present in mucosal lining of genital tract are the first cells to encounter with HIV. Dendritic cells uptake viral particles present it to T or B lymphocytes and facilitate particles in cell to cell transmission. Mature dendritic cells retain infectious HIV particles into a pocket-like compartment which is

physically connected to the cell surface. The intact viral particle in compartment can infect T cell at cellular interference. The binding of dendritic cells to CD4 cells may results in migration of virion in pockets across synapse (McDonald *et al.*, 2003).

Treatment

If there is anything we are sure about treatment for AIDS, it is that there is no treatment for AIDS. Prevention and carefulness is the only safe and reliable measures that can help HIV-positive patients to cope with the illness. Being careful of unsafe sex, untested blood transfusions, used syringes, and, especially fighting with 'associated diseases' (means not troubling the immune system) are tools that can increase the life expectancy.

Although there is no cure for AIDS, but there are medicines available which can fight against HIV at certain level. These treatments may reduce HIV load in human body but key to decrease complications in keeping the immune system healthy. Normally, there are three main factors that are taken into account before devising a strategy for treatment:

- Is the patient willing and prepared for therapy?
- What is the stage of disease?
- Does the patient have any other health related issues? (<http://aids.gov/hiv-aids-basics>)

A medicine with the name of AZT became the first clinically approved and permitted treatment for HIV disease, in 1987. Over the years, approximately 30 other drugs are declared appropriate to use for treating patients that are living with AIDS. Research is being carried out till now and many drugs are under development stage.

These drugs are called by different names and categorized in different groups such as:

- "The Cocktail" (combination of different drugs)
 - Antiretroviral (ARVs)
 - Highly Active Antiretroviral Therapy (HAART or ART)
- Intake of a single drug will not have any considerable effect on HIV viral activity, and it would keep on damaging the immune system. However, taking 3 different drugs simultaneously can contain the growth of HIV, and protect the immune system as well.

We will now look further into the treatments of AIDS:

Reverse transcriptase inhibitors (RTIs)

They are regarded as first group of antiretroviral drugs to treat HIV. As their name implies, they inhibit the action of reverse transcriptase, a DNA polymerase, which replicate the HIV frame.

Mechanism of RTIs

These drugs act by interfering with the production of a new segment of proviral DNA. Reverse transcriptase uses an NRTI or NtRTI triphosphate instead of using a natural nucleotide supply to the cells. These drugs have little

difference in their structure to that of natural nucleotides therefore; they can form the chemical bonds necessary to add those natural nucleotides (Moyle, 2000).

These are RTIs are further divided into three types:

1. Nucleoside analog reverse-transcriptase inhibitors (NARTIs or NRTIs)
2. Nucleotide analog reverse-transcriptase inhibitors (NtARTIs or NtRTIs)
3. Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)

All NRTIs and NtRTIs have a similar mode of action, these drugs are analogues of deoxynucleotides which are present naturally and are required for the synthesis of viral DNA. Therefore, they come in competition with them for incorporating with viral DNA chain while elongating naturally. NRTIs and NtRTIs do not have a 3'-hydroxyl group on the deoxyribose moiety, which distinguishes them from natural deoxynucleotidal substrates; therefore, the next incoming deoxynucleotide is unable to form the next 5'-3' phosphodiester bond essential to extend the DNA chain, following incorporation of an NRTI or an NtRTI. This causes the processing of viral DNA, which is also known as chain termination, to halt when NRTI is incorporated. All NRTIs and NtRTIs are categorized as competitive inhibitors of different substrates (Goldschmidt *et al.*, 2014).

NNRTIs have altogether a distinctive mode of action as compared to NRTIs. NNRTIs directly bind with the enzyme to block its activity. The movement of protein domains of reverse transcriptase is constrained by the action of NNRTIs. These domain movements are necessary for the synthesis of DNA. Due to this type of activity, NNRTIs are classified as non-competitive inhibitors of reverse transcriptase (Kakuda, 2000; Herschhorn *et al.*, 2010).

Risks involved in RTIs treatment

NRTIs and NtRTIs can hinder the mechanisms of human cells, by blocking the reverse transcription. There is always a risk involving the uptake of NRTI or NtRTI triphosphates when the host cells start to reproduce, this is mainly due to the reason that these chemicals mimic structure wise with natural building blocks of DNA. DNA polymerase, which is the corresponding human enzyme, has quite less affinity than reverse transcriptase for attachment with NRTI/NtRTI triphosphates, therefore many researchers say that it is not a big problem. Also, human cells are equipped with machineries to recognize and rectify mistakes in DNA synthesis.

However, NRTIs do have side-effects which involve damage to the specific DNA present in mitochondria. Mitochondrial DNA also must be copied when a cell under goes division, a process carried out by an enzyme called polymerase-gamma (the enzyme for replication of

mitochondrial DNA). This enzyme has high affinity for RTIs, which makes mitochondrial DNA vulnerable to these drugs. Symptoms thought to be related to mitochondrial damage include lactic acidosis, lipodystrophy (fat loss in the face and limbs), and peripheral neuropathy (Lewis *et al.*, 2006).

Transplantation of transgenic stem cells

The HIV-1 entry into the host cells requires the interaction of the viral envelope with the CD4 surface molecule and certain co-receptors, which are represented by the chemokine receptor, CCR5. Suppression of HIV-1 replication can be highly effective by the interaction of CCR5-tropic HIV-1 by small-molecular antagonists (Hütter *et al.*, 2009).

In 2009, an HIV patient with acute myeloid leukemia was reported to have achieved long-term control of HIV-1 after allogeneic hematopoietic stem cell transplantation (alloHSCT) from a human leukocyte antigen. Control of HIV-1 with stem cell transplantation raised feasibility of HIV control and removal by stem cell transplantation based techniques. It is also reported that alloHSCT without the use of ART cannot be so helpful. For this therapy to be successful and more effective, it should be used in combination with antiretrovirals. Transplantation of CCR5-negative donor cells to CCR5-positive recipients illustrates that removal of the primary target cells can be sufficient to prevent a rebound of viral replication (Hütter *et al.*, 2009).

Introduction of resistance-conferring genes into stem cells before transplantation is still another approach to enhance HIV resistant stem cells. This technique is attractive in a way that it may become 'once in a life-time' treatment. It can also help to lessen the use of ART and the side effects caused by them (Hütter *et al.*, 2009).

The therapeutic gene used for the transplantation should have a selective advantage to allow the expansion of the transgenic cell pool *in vivo*, so that it can replace virus-susceptible cells. This can be effectively achieved by targeting steps in the viral life cycle that protect the transgenic cells from the cytopathic effects of viral components produced inside the cell.

Another approach may include targeting of the steps before integration and inhibition of entry of virus. This method can also decide the fate of hematopoietic cells that carry transgenes directed against different steps in the viral life cycle. Studies have shown that, using transgenic T cells without conditioning regimen were tolerable and had long-term survival of marked cells in some samples. Moreover, gene therapies can also be helpful in treatment of HIV, approaches such as allogeneic transplants can obviate the need for laboratory conditions of high safety levels (Hütter *et al.*, 2009).

Epigenetic silencing of HIV by histone methylation

Epigenetics refers to the genetic control of genes that determine which genes need to be turned on or off and also which proteins need to be transcribed in certain circumstance. This phenomenon is executed by certain factors other than an individual's DNA sequence. In other words, epigenetics contributes to differential expression (Simmons, 2004). Three systems interplay with each other to silence certain genes inside a cell, these include DNA methylation, histone modification and RNA-associated silencing (Egger *et al.*, 2004).

In case of HIV, latency or silencing of provirus is due to deacetylation and methylation of histones located at long terminal repeat of viral genome. It is well established that inhibition of histone deacetylases (HDACs) trigger the reemergence of HIV from latent phase while the input of histone lysine methyltransferases (HKMTs) in maintaining HIV latency phase still remain uncertain. Extensive genome-wide analyses have shown that histone methylation can lead to the activation or repression of genes, depending on histone lysine residues and whether they are mono-, di-, or trimethylated (Friedman *et al.*, 2011). HIV is termed as a persistent pathogen because it exists in a small population of resting memory CD4⁺ T cells (Finzi *et al.*, 1999)^[24] and tissues (Yukl *et al.*, 2010) although in latent state but in the form of replication-competent provirus. This property of low-level HIV replication in certain anatomical sites which may be comparatively inaccessible to drugs attributes to its persistence even in antiretroviral therapies (Cory *et al.*, 2013; Palmer *et al.*, 2011). In other words, the latent infection of HIV is unaffected by ARTs and remains hidden from the immune system (Archin *et al.*, 2014). In summary, epigenetic silencing of HIV provirus is a general feature of all persistent HIV infections and hence proves to be the major obstacle towards finding a functional cure for HIV infection. Therefore, current efforts have been focused on the development of therapies to disrupt latency to make virus accessible to drugs without any deleterious effect on systemic inflammatory responses of the host. Reactivation of proviruses in the presence of antiretroviral therapy is expected to make them visible to the host immune system and this ultimately leads to the clearance of latently infected cells (Mbonye *et al.*, 2014).

Practically, eliminating the latent provirus reservoir is not easy because it is extremely stable with an estimated half-life of 44 months (Siliciano *et al.*, 2003), being established early during infection (Chun *et al.*, 1998) and is being continually replenished during each episode of viremia (Chun *et al.*, 2005) or by replacement of latently infected cells through homeostasis (Chomont *et al.*, 2009). The remarkable fact that intensification of antiviral regimens in infected host have no effect on removal of this latent reservoir (Dinso *et al.*, 2009) provokes a pressing need to develop a novel therapy with capacity to

purge the pool of latent provirus reservoir (Richman *et al.*, 2009; Trono *et al.*, 2010).

Polycomb repressive complex-2 (PRC2) is the only moiety in mammalian cells that is able to catalyze the di- and trimethylation of H3K27 (H3 Lys27 trimethylation) (Margueron *et al.* 2011). Kuzmichev *et al.*, (2002) has demonstrated that EZH2, the enzymatic component of PRC2 which is responsible for the formation of H3K27me₃, contributes to the establishment and maintenance of transcriptional silencing of HIV. Further, knockdown of EZH2 not only induces latent HIV proviruses, but it also sensitizes latent proviruses to stimulation by exogenous signals and limits transcriptional silencing. However, DZNep (3-deazaneplanocin A; histone methyltransferase inhibitors) can act cooperatively with the histone deacetylase (HDAC) inhibitor to activate HIV transcription (Tsai *et al.*, 2010).

Novel strategies to cure HIV latent provirus pool should be equipped with nontoxic molecules that can induce its transcription and target host cells for destruction. The strongest existing candidate molecules for this role are HDAC inhibitors, such as SAHA and valproic acid (Archin *et al.*, 2009; Lehrman *et al.*, 2005; Ylisastigui *et al.*, 2004).

CONCLUSIONS

Although Recombinant Transcriptase Inhibitors (RTIs) and stem cell transplantation are currently being used as the most effective treatment against HIV as they significantly inhibit the replication of HIV. However, the persistence of HIV in host genome remains an obstacle in secure therapy and patient's life rely on continuous supply of RTIs. Development of novel therapies based on epigenetic silencing and RTIs seems to be inevitable tools to concentrate upon.

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