

Gene Silencing: A Novel Approach and Suppression of HIV-1 Gene

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Abstract

In today's era, AIDS (Acquired immune deficiency syndrome) has been changed from a death sentence to a manageable chronic disease after usage of antiretroviral therapy (ART). Although, according to NACO 2015 and UNAIDS 2017, there was a 54% decline in AIDS death from 2007 to 2015 and an overall 32% decline in new HIV infection (80,000 in 2016). It is still one of the leading causes of death. UNAIDS (2017) reported 2.1 million (1.324 billion) people living with HIV in India and with a ranked third in the world.

Keywords: Gene silencing; HIV viremia; HERVs

Introduction

In today's era, AIDS (Acquired immune deficiency syndrome) has been changed from a death sentence to a manageable chronic disease after usage of antiretroviral therapy (ART). Although, according to NACO 2015 and UNAIDS 2017, there was a 54% decline in AIDS death from 2007 to 2015 and an overall 32% decline in new HIV infection (80,000 in 2016). It is still one of the leading causes of death. UNAIDS (2017) reported 2.1 million (1.324 billion) people living with HIV in India and with a ranked third in the world. In HIV patients, HAART is currently being used to suppress viral replication and viral load. HAART regimens significantly prolong the lives of HIV patients [1]. But the virus cannot be removed from the proviral stage. Thus, the latent proviral cell is reactivated to produce HIV viremia as ART treatment is stopped [2-5]. Present HIV treatments inhibit viral replication by preventing viral latency [6]. Epigenetic processes can silence the proviral virus and inhibit the spread of infection [6]. In HIV life cycle, the reverse transcriptase enzyme uses the viral RNA and DNA of the host cell to synthesize the proviral DNA. Followed by this proviral DNA inserts itself into the nucleus of the host cell, thereby enabling proviral DNA to duplicate during cell division. However, present treatment could not eliminate the pro-viral DNA. Human endogenous retroviruses (HERVs) have similar genetic structures to HIV-1. Some HERV virus is transcriptionally active remaining are silenced and defective. For example, HERV-K retains all open reading frames, suggesting the potential infectivity after reactivation under certain conditions. It is known that in germ cell HERVs are transcriptionally active during germ cells and become permanently silent during embryonic development [7,8]. In HERVs, long lasting silencing and time of silence is determined by DNA methylation [9-13].

Discussion

DNA methylation is a chemical modification which is regulated by enzyme DNA methyltransferase (DNMT). DNA methylation inhibits transcription factor to access DNA, bind to promoters and switch off the gene expression. Genomic imprinting results in a gene expressed in inherited chromosome either from one or another parent. Genomic imprinting affects gene expression either by chemical modification of DNA or alteration in chromatin structure. When this normal process is combined with the genomic mutation. It results in disease development. Genomic imprinting is an epigenetic phenomenon, in which the actual gene sequence remains unchanged by epigenetic modification (DNA or Histone Methylation) but the gene transcription process gets altered, resulting in an expression of only one inherited copy of the imprinted gene in the embryo. It is a heritable change in the gene function that

occurs without a change in the DNA sequence. Many diseases are regulated at early growth and development stage by allele-specific alterations in DNA methylation at differentially methylated regions (DMRs) and fetal development are due to genetically imprinted genes. DNA methyltransferase (DNMT) adds the Methyl (-CH₃) group to cytosine of CpG islands and synthesizes methylated DNA. Promoter region contains CpG islands. DNA methylation occurs in the promoter region which affects the gene expression in mammalian. Many *in-vitro* and *in-vivo* studies have shown that the 5'Long terminal repeats (5'LTR) of HIV-1 is recognized by a transcription factor to HIV-1 transcription silencing [14-18]. In addition, progeny inherits DNA methylation. The methylation of the targeted gene could make long term gene suppression [19-21]. A study conducted in Spain population was reported that chimeric protein (N-terminal of HIV integrase) inhibits HIV-1 expression with the C-terminal domain of DNMT3b [6]. Though, the safety of this approach is of great concerns as N-terminal of integrase enzyme is not conservative. Previous studies have been reported that the conserved region of HIV is targeted by four zinc-finger proteins (ZFP) [22-26].

Conclusion

Deng et al. reported a fused ZFP, that was designed to target HIV-1 5'-LTR, to DNMT1 in order to methylate the CpG islands in 5'-LTR, to reach a long-term silencing of the HIV-1 provirus. They also tested ZF2-DNMT1 fusion protein on HIV-1 infected or latently infected cell culture models and found that chimeric ZF2-DNMT1 can induce stable suppression of HIV-1 provirus by adding a methyl group to the targeted CpG islands in 5'-LTR. These evidences suggest the DNA methylation play an important role in silencing of proviral DNA. This approach may provide a new way of HIV-1 proviral gene expression suppression with hope to replace daily HAART. Limited evidence is available about this approach. Hence, further studies should be done on methylation of HIV-1 LTR.

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