

HIV and Reverse Transcription

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There are many steps in the process of retrovirus infection. The virus enters the host's T cells where it uses the host's replication machinery to replicate itself. After replication the virus is embedded into the host DNA. The viral DNA holds the information for the components of the virus including the viral RNA, reverse transcriptase, and other proteins that are essential to viral proliferation. This review looks at inhibiting the transcription process as it pertains to HIV-1.

Introduction

In 1981 AIDS, caused by HIV, became known to the world. AIDS is particularly harmful in that it inactivates or destroys the CD4 lymphocytes in the body (Lewthwaite, 2009). CD4 lymphocytes are key cells that fight infections. Infections that a healthy human without AIDS acquired become deadly. Human Immunodeficiency Virus works by invading the host's T cells to use its replication proteins for proliferation. HIV has embedded in its envelope, proteins that have an affinity to the receptor protein, CD4 embedded in the cell membrane of the T cells. Interaction between the envelope proteins and the CD4 receptor proteins allows for the endocytosis of the virus into the T cell. Once inside the cell the capsid essentially dissipates freeing the viral RNA, which is pre-attached to reverse transcriptase, and other viral proteins one in particular integrase. The viral RNA is then reverse transcribed into single stranded DNA with several mutations due to reverse transcriptase's poor proof reading. The single stranded DNA is again reverse transcribed into double stranded (ds) DNA. The enzyme integrase associates with the dsDNA and transports it through a nuclear pore into the nucleus. Integrase then incorporates the viral DNA into the host DNA to be transcribed. The host's polymerase transcribes the viral DNA into messenger RNA that is shuttled to ribosomes on the Rough Endoplasmic reticulum to be synthesized into proteins. The RNA codes for all pieces of the virus: reverse transcriptase, integrase, proteins for capsid and matrix, and protease. These pieces are put together in a complex that is moved to the cell membrane. This is where two RNA-RT complexes and multi-protein

chains exocytose with envelope proteins to make an immature virion are created. The immature virion contains enzymes called proteases that cut the multi-protein chains, allowing those proteins to form the capsid and matrix that surround the RNA-RT complex, which is now mature (Herschhorn, 2010).

HIV Treatments

The mortality rate has increased 80% in industrialized nation due to Highly Active Antiretroviral Therapy (Lewthwaite, 2009). This therapy includes five types of drugs, which are thus: Nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors, entry inhibitors, and integrase inhibitors (Lewthwaite, 2009). Recent biochemical engineering has brought forth a new type of treatment. It is similar to the reverse transcriptase inhibitors in that it imbeds itself into the DNA sequence at a nucleoside analog. However the chemical, kp-1461/1212, can switch between two tautomers allowing it to associate with G and A nucleotide bases. This increases the genomic errors. Research into kp-1461 has been subdued for reasons unknown but initially the drug looked promising. NRTIs are novel in the way that they have a normal 5' end for attachment to the viral RNA however the 3' end is altered so that continued nucleoside addition is not possible. NNRTIs work in a different way. The protein complex needed for RNA reverse transcription exists in two conformations (Li, 2008). The closed for is the only way that reverse transcription can be initiated. NNRTIs fit into a pocket in this complex locking it into

the open position, which keeps reverse transcription from happening.

Complications

If all HIV virions were active then the NRTIs and NNRTIs are exceptional treatments to eradicating HIV. However, HIV has a dormant state that allows it to stay alive, but not replicate. Targeting dormant HIV is very difficult and solutions are still being sought after.

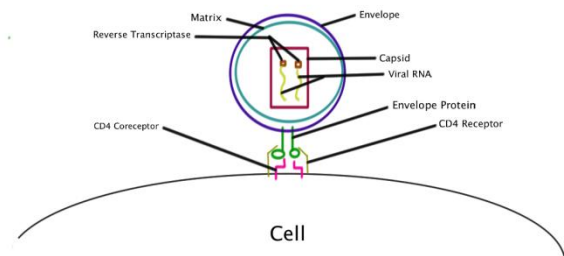


Figure 1: This diagram shows HIV Attached to cell via envelope proteins that have an affinity to CD4 receptor proteins on the surface of T Helper cells. A conformational change in the coreceptor pulls the viral envelope close to the cell allowing it to coalesce bringing the viral capsid and matrix into the cell.

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