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THE REPLICATION MECHANISM OF HIV: MOLECULAR INSIGHTS, HOST CELL TARGETS, AND THERAPEUTIC INTERVENTIONS

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Abstract: Human Immunodeficiency Virus (HIV), a single-stranded RNA virus from the Retroviridae family, is the causative agent of Acquired Immunodeficiency Syndrome (AIDS). HIV primarily targets immune cells, particularly CD4+ T-helper cells, macrophages, and dendritic cells, using specific surface glycoproteins and co-receptors (CCR5 and CXCR4) to enter host cells. Its life cycle is dependent on three essential viral enzymes: reverse transcriptase, integrase, and protease. These enzymes facilitate the transformation of viral RNA into DNA, its integration into the host genome, and the production of mature infectious particles. This article provides a comprehensive overview of HIV's molecular replication strategy, the role of host cell receptors, and the mechanism of novel antiviral agents such as lenacapavir.

Keywords: HIV, AIDS, Retrovirus, Reverse Transcriptase, Integrase, Protease, CD4+ T-helper Cells, CCR5, CXCR4, gp120, gp41, Lenacapavir, Viral Replication, Host-Pathogen Interaction

1. Introduction

HIV is a globally significant pathogen that causes chronic infection and progressive immune system failure. It belongs to the Retroviridae family and is characterized by its reverse transcription mechanism, where the viral RNA genome is converted into DNA inside the host cell. The virus has a lipid envelope derived from the host membrane, and its inner core contains viral RNA along with essential enzymes for replication.

There are two main types of HIV:

HIV-1: The most common and virulent form worldwide.

HIV-2: Less transmissible and largely confined to West Africa.

2. Structure of HIV

Envelope: Composed of a host-derived phospholipid bilayer embedded with viral glycoproteins gp120 and gp41.

Capsid: Protein shell made primarily of the p24 protein, enclosing two copies of single-stranded RNA.

Enzymes within the virion:

Reverse Transcriptase

Integrase

Protease

3. HIV Entry into Host Cells

3.1 Target Cells

HIV primarily infects:

CD4+ T-helper cells

Macrophages

Dendritic cells

These cells are crucial for initiating and regulating immune responses. Destruction of CD4+ T cells leads to immune suppression, making the host vulnerable to opportunistic infections and cancers.

3.2 Receptor and Co-receptor Binding

gp120 binds to the CD4 receptor on the host cell.

This induces a conformational change in gp120, exposing binding sites for:

CCR5 (used in early-stage infection)

CXCR4 (used in advanced stages/AIDS)

gp41 mediates the fusion of the viral and host cell membranes, allowing the viral capsid to enter the cytoplasm.

3.3 Role of Co-receptors

CCR5: Directs immune cells to inflammation sites. Individuals with a genetic deletion (CCR5-Δ32) are resistant to HIV-1 infection.

CXCR4: Involved in hematopoiesis and immune cell signaling. Viruses that shift to using CXCR4 tend to cause rapid disease progression.

4. HIV Replication Cycle

4.1 Reverse Transcription

The enzyme reverse transcriptase synthesizes complementary DNA (cDNA) from viral RNA. This process includes:

RNA-dependent DNA synthesis

RNase H activity to degrade the original RNA strand

DNA-dependent DNA synthesis to produce double-stranded DNA

4.2 Integration

The enzyme integrase transports the viral DNA into the host nucleus and incorporates it into the host genome. Once integrated, the viral DNA is known as a provirus and can remain latent or become transcriptionally active.

4.3 Transcription and Translation

The proviral DNA is transcribed into viral mRNA by the host RNA polymerase II. These transcripts are then translated into viral proteins, including polyproteins.

4.4 Proteolytic Processing

Protease cleaves long polyprotein chains into functional viral proteins required to assemble new virions.

4.5 Assembly and Release

New viral RNA and proteins are assembled at the cell membrane, where the virus buds off. The virus acquires its envelope from the host cell membrane, completing the replication cycle.

5. HIV Pathogenesis

As the virus replicates, the immune system becomes progressively weakened:

Acute phase: Flu-like symptoms, rapid viral replication, and temporary decline in CD4+ count.

Chronic phase: Asymptomatic period where the virus remains active at low levels.

AIDS: CD4+ count drops below 200 cells/μL, leading to severe immunodeficiency.

6. Therapeutic Interventions

6.1 Antiretroviral Therapy (ART)

ART involves a combination of drugs that target different stages of the HIV lifecycle:

NRTIs/NNRTIs: Inhibit reverse transcriptase

Integrase inhibitors: Block integration of viral DNA

Protease inhibitors: Prevent maturation of viral proteins

Fusion and entry inhibitors: Block viral entry into cells

6.2 Lenacapavir

Lenacapavir is a capsid inhibitor that:

Binds to the viral capsid protein

Disrupts capsid stability

Blocks nuclear import and genome integration

Interferes with capsid disassembly during infection

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