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A Complete Review Upon Modern Highlights on HIV DNA Integration

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Abstract: Living cells are complex organisms sharing simple tasks across a variety of levels to get their desired nutrition. HIV - 1 is no exception to this, it too requires to perform a number of events to aid the propagation. Unlike conventional methods of proliferation, HIV - 1 had involved tricky ways for their survival. Following this paradigm, beginning with anchoring, uncoating, reverse transcription, integration, synthesis of genetic compounds release. Having done that the HIV - 1 retroviruses cause a spike in the infectious state and show a surge in the clinical outcomes. Therefore, integration has been found to build the turf of HIV - 1 inside the host cell network. Two steps - (a) 3' end processing & (b) DNA strand transfer are gone through for the feasible accomplishment of integration. In this several host cells, structural, chromatin cell proteins take part. Overall, these factors, only harmful proteins like Integrase (IN), RNase H have their eminent participation. Other functionally efficient proteins (LEDGF/p75, EED, Ini - 1) pledge their effort in the integration. Being a seemingly crucial phase in the HIV - 1 life cycle integrase has been our area of integrase in this whole review. The entire information is provided against legitimate literature. To tell briefly, HIV - 1 progresses to form its reserve transcribed DNA with the host DNA following the integration mechanism.

Keywords – HIV-1, Retrovirus, Integration, Integrase (IN)

Introduction

The DNA which belongs to a viral genome body shows their interest to integrate the host cell body by duplicating or applying to copy them. That scene makes a situation of replicating the DNA proviral part which connects with the cellular portion of DNA in the division moment phase.These types of similar looking genes are observed in any kind of animal host cells which stand in normal formation. Proviruses are experts at mimicking transcription procedures and perform it very finely, so they act like viral RNA to transcript in a proper scenario. Viral RNAs manage to build a stair where RNAs can instigate to assemble with viral proteins, whereas the half amount of RNAs (strands with their full length) is

being conducted to transport their young to mobilise the genomic RNAs for function[1].

One of the vital enzymes which performs in cell structure is Reverse Transcriptase. viral RNA and few proteins that bring the Virus-encoding IN proteins to take up the host cells during infections and that proteins facilitate integration mode which end up in the viral core. Whenever the generation of viral DNA begins their reverse transcription, they enclose them into the cytoplasm and form proteins such as nucleotides and nucleoprotein complexes along with an molecular weight (excessive) that is pushing the nucleus to search for more integration routes.

While it might occur anytime throughout the host genome, integration occurs directly at the viral DNA's termini. Essentially most of the genomic portion of DNA positions can be used for integration acceptor location, there are a few particular ones. Retrovirus groups exhibit individual characteristics based on regional preferences. Certain preferences seem to involve chromatin-associated items that have been furnished with IN functionally. Retroviral insertion in gene therapy is being linked to adverse effects, especially integration near proto-oncogene.

Among the myriad kinds of pathogens, retroviruses possess the sole characteristics of recombining their respective genetic materials to the host cellular machinery. Specialised features of retroviruses for genetic recombination occur via enzymes. Now enzymes like Reverse Transcriptase (RT) & Integrase (IN) along with viral nucleocapsid protein make-up the HIV-1 virion particle. While moving through the cellular network the virion particle goes through a number of cellular alterations like after getting an entry in a deeper cellular network the viral core from that virion particle is ejected into the cytoplasm. HIV-1 RNA is being converted by Reverse Transcriptase enzymes and creates duplicates where one dsDNA forms RT Complex which stands as the main core of the viral genome.

When HIV travels a host cell and discharges its RNA genome, the integration process begins. The virus converts its RNA into complementary DNA, also known as cDNA via employing the enzyme reverse transcriptase. Within a pre-integration complex, this viral cDNA gets transported to the nucleus in the host cell. The procedure is also known as 3'- end processing where the integrase kicks inside and prepares the viral DNA. In that scenario, a process named strand transfer, the enzyme catalyses the viral DNAs insertion into a region through the host genome. The provirus belongs as a stable genetic segment created through this insertion, corresponding to the host DNA across cell division.

This review embraces data from both HIV and animal retroviruses, as both have helped lead to major improvements. First this article goes over the evolution of retroviral integration modules, current biochemical steps and integration in the cellular atmosphere.

Historical roadmap

- Uncovering the HIV - Following the progression of virology through the able hands of renounced scientist, the team of Luc Montagnier(1983) and subsequently Robert Gallo's team from U.S discovered the Human Immunodeficiency Virus. That discovery stimulated the interest about how HIV spreads into the cells and deteriorates one's health.

- Retrovirus and Reverse Transcription - Retroviruses are those organisms which have the ability to commence Reverse Transcription (conversion of RNA into DNA). HIV falls in this group of retroviruses. In the early seventies, a number of viruses resembling HIV like the Rous sarcoma virus placed the founding stone for the proper visualisation of retroviruses similar to HIV. Furthermore such intensified studies prove the proviral DNA is integrated into the host genomes, which laid the framework for modern therapeutic advancements.

- Integration by HIV - Following the roadmap brought by intensive research conducted by early seventies, scientists came up with the answer concept that said HIV in its entire life cycle within the host system manages to assimilate its own unique genetic material (DNA) with the genome of a host cell. Lately the role of the HIV related enzymes was proposed to be responsible for integrating viral DNA into the host genome. So the integrase enzymes bring into its action by attaching to the proviral DNA terminals which further smoothens the integration with host cell DNA.
  When the integration process gets completed, it allows the complete occupancy of that viral DNA to be incorporated into the host cell's DNA. Then HIV's next goal becomes to synthesise fresh viral components via hacking the host cellular system. The host cell's genome makes the newly inserted viral genetic material an inseparable part of it. There the viral genetic components can remain dormant for a significant amount of time which is also termed as latency of HIV. Because of such behaviour shown by HIV, we can count HIV infection as a chronic ailment.

- Elucidation of integrase's microscopic structure - With more and more time spent in the evaluation (microscopic) of integrase exposed integrase's functional group preferences and as well as affinities for the viral and host genome. Later on, researchers discovered the partial nature of HIV towards transcriptionally active genome sites while looking for regions to integrate[2].

Structural biology of HIV

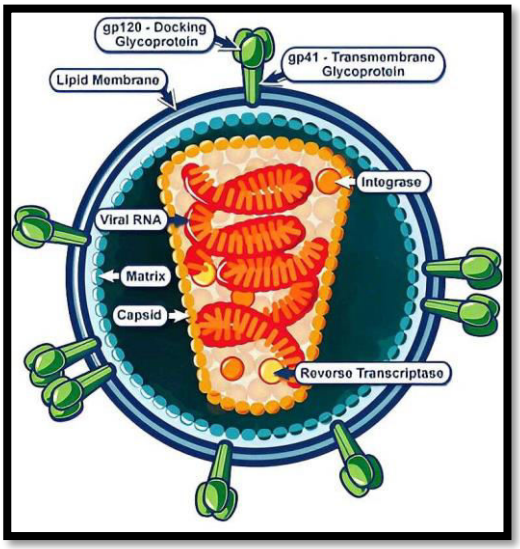

Fig (1) : Structural Make-up of HIV

The appearance of HIV was brought under the lens after analysing immunodeficiency viruses over the past decades[3],[4]. Around 30 million across the world are carrying retroviral infections caused by HIV-I and its relatively less infectious kin HIV-II belonging to the family Retroviridae. Though other than its fellow mate HIV2, HIV1 possesses the potential of encoding just a handful of proteins[5]. By altering the host's cellular factors, the HIV-I retrovirus forms an immature virion after binding with the cellular surface receptors[6]. HIV-I is under the exploratory panel for the recent years.

Though the host immune machinery intensively targets the replication component, the retrovirus (HIV-I) manages to subvert the host resistance[6]. For this very reason the therapy against retroviruses couldn't be termed a huge success. So, a highly active antiretroviral therapy or HAART was established whose main focus was on the inhibition of IN and RT (protease and Reverse transcriptase) enzymes. The HAART became a widely chosen option to bring down viable retroviral count and rapid transmission substantially. Still researchers are puzzled with the recent emergence of resistant strains.

Mechanism of action of HIV

HIV (Human Immunodeficiency Virus), a retrovirus using RNA as it's genetic material instead of DNA, targets the human immunological system, specifically CD4 positive T cells or Helper T cells, a type of white blood cells, which prominently aid in immune defence by stimulating other cells such as macrophages, CD8 T cells and B cells to fight infections.

If left unattended, HIV infection gradually weakens the immune system by depleting the CD4+ cells, causing the body to be more susceptible to serious opportunistic infections and furthermore, may lead to cancer formation, and in the worst-case scenario, HIV advances to establishment of a sophisticated Immunological disorder known as AIDS (acquired immunodeficiency syndrome), the most advanced stage of HIV infection, that is not treatable and a communicable infection tending to spread through exchange of bodily fluids, needles or contaminated blood transfusions, which is indicated by symptoms like severe flu and drastically lowered T cell count.

The mechanism through which HIV targets the immune system is listed below proficiently in several simple steps-

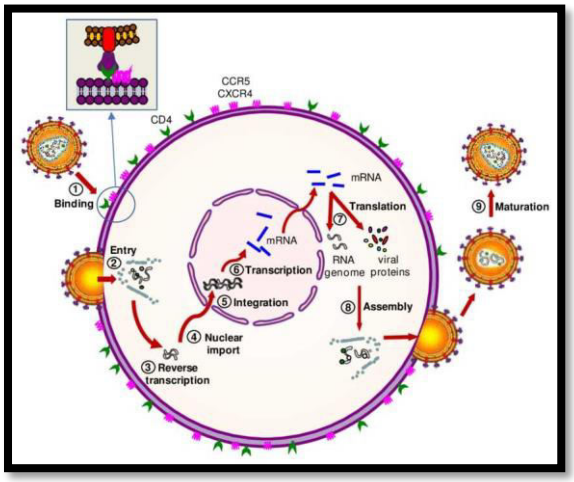

Fig (2): Mechanism of Action of HIV

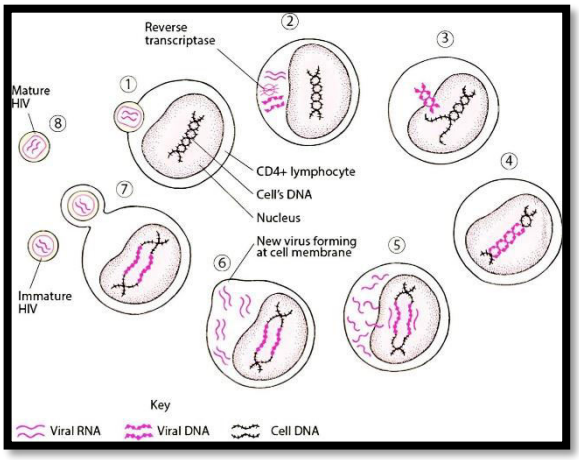

Fig (3): Life Cycle of HIV[28]

1. **Attachment and Entry:** HIV entering the host body is the most crucial step in its lifecycle. HIV viral glycoprotein gp120 then binds with CD4+ T cells present on the surface of the target cell in the CD4 receptors, triggering the conformational change in gp120, enabling it to bind to either CCR5 or CXCR4 co-receptors[7], depending upon the virus strain. Post co-receptor binding, viral glycoprotein gp41 exhibits structural alterations enabling the viral envelope to merge with the host cell membrane. The resultant of this merger is the formation of a crater, facilitating the discharge of the viral capsid into the cytoplasm. The capsid consisting of the HIV RNA genomic sequences and enzymes are eventually transported into the host cell for the initiation ofthe next steps for replication process.

2. **Reverse Transcription:** In this process, the single stranded HIV genome transforms into double stranded DNA, enabling it to be incorporated into the host genome. Viral enzyme Reverse Transcriptase (RT) facilitates this process, performing 2 essential functions- RNA-dependent DNA polymerase and RNase H. HIV RT produces minus strand DNA utilizing viral DNA as a scaffold and Host tRNA primer. RT-RNase H activity annihilates the DNA-RNA hybrid by demolishing the RNA strand. The minus strand is then used to synthesize the plus strand resulting in the yield of the double stranded viral DNA. Pre integration complexes (PIC) are formed as the double stranded viral DNA interacts

with viral proteins such as integrase, which is further transported to the nucleus for integration.

3. **Integration:** Integration is the critical phase in the cycle of viral replication, allowing the virus to form a long-term infection by inserting the DNA into the host cell genome. This process is facilitated by integrase cutting the 3' ends of the viral DNA exposing the -OH group, prepping it for integration. Both the host and viral DNA are then linked by the integrase enzyme, identifying the areas active transcriptionally for integration[8]. The 3' ends of the viral DNA assault and link with the host DNA in a strand transfer event[9]. The host cell then repairs enzyme fill and seal the craters at the site of integration to complete integration process[8],[9].
4. **Transcription & Translation:** These mechanisms generate viral DNA and proteins in the host genome from the integrated proviral DNA. Host RNA polymerase II commences transcription at the 5' long terminal end activated by the transcription factors like viral Tat protein and NF-kB. This generates full length viral DNA, some of which act as genomes for new virions whilst others are cleaved into smaller mRNAs for encoding viral proteins. Meanwhile, Translation takes place in 3 phases- firstly, Full-length RNA is translated into Gag structural proteins and by ribosomal frameshifting Gag-Pol enzymes (reverse transcriptase, integrase, and protease) followed by cleaving of mRNAs encode gp120 and gp41, translated, glycosylated, and delivered to the membrane for assembly and cleaved mRNAs encode Tat, Rev, and Nef for controlling replication and immune evasion[10].
5. **Assembly:** It entails packaging the Gag and Gag-Pol proteins unified within the viral core with the RNA genome. The viral membrane is embedded with Env glycoproteins with the host cell encapsulates the emerging virion and the virus preps for infecting other cells after the viral protease degrades the polyproteins.
6. **Budding & Maturation:** When the host cell is abandoned by a freshly generated virion carrying Viral genomic data and proteins, budding occurs[11].A lipid envelope and Env glycoproteins (gp120 and gp41) are accumulated as the virion continuously grows through the host cell. The viral protease cleaves the Gag and Gag-Pol polyproteins required for the viral maturation, which happens to reorganise the viral core rendering it infectious. The mature and stable virus can then repeat replication cycle spontaneously and infect new host cells continuously.

Manifestation of HIV within the host

HIV 1 retrovirus finds its entry through the loosely organised blood transfusion and unprotected sextual activities and sometimes direct transmission through blood circulation. Like that of other viruses, HIV-I has several spikes on its outer envelope. The proteinous spikes contain heterodimers made of glycoprotein gp120 and glycoprotein gp41[12]. At the entry level, the HIV-I simulates its proteinous spikes to bring a myriad of confirmation alteration which builds a broad channel in between the host and viral cell surfaces. This is how HIV-I lodgesits viral core inside the host cell cytoplasm. We had mentioned earlier that the principal targets of human immunodeficiency virus I are macrophages along with clusters of differentiation lymphocytes (CD4+ T cells). When the CD4 interacts with surface glycoprotein gp120 a flexible conformational change occurs enabling the confluence of both the inner domain and outer domain of the structural glycoprotein gp120 monomer. This procedure follows the expression of a new binding site for the cell surface molecule (secondary) and the mostly observed cell surface receptor turns out to be CC-Chemokine Receptor 5 (CCR-5). The creation of a fresh binding site initiates the insertion of an entry of fusion peptide from gp41 (Transmembrane Glycoprotein). After that inside glycoprotein 41, Amino and Carboxy - terminal heptad repeat sequences reshuffle their dimerised framework. These successes with the junctioning between viral and host cell networks[5].

Elaboration of CD4 - gp120 relationship

Abroadened view on the surface glycoprotein - CD4 interaction provided the seed of designing target specific antibodies. Disulfide bonds were inserted in the place of gp120 - CD4 confirmation to form a calm and stable approach of HIV 1 deactivation through bringing changes in CD4 attachment. Again, extensive remodelling was used for shadowing the sites placed exterior to specific CD4 binding.

A perfect picturisation of CD 4 binding sites just stroke lighting in researchers' heads as it became clear that the antibodies from modified B cell clones (obtained by injecting redesigned CD4 - gp120 interface and peripheral mononuclear cells of HIV infected persons) showed rays of hopes in potent neutralisation of retroviral pathogens. A long note retained on such antibodies said that the neutralising capability of those antibodies come from imitating the CD 4 by the help of their epitopes. That technique is so smooth that it perfectly fits the gp120 - CD4 interaction site.

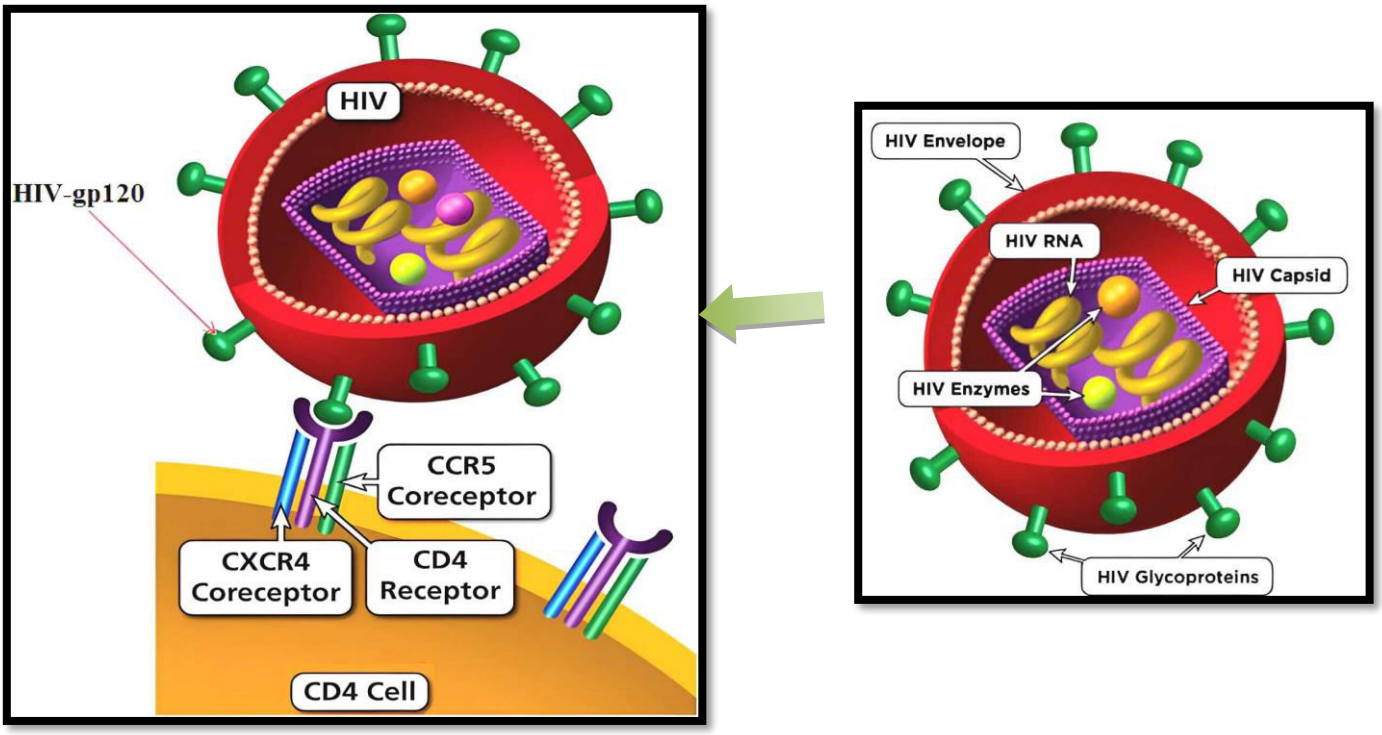

Fig (4): Role of CD4 Receptors and Co-receptors in HIV Proliferation[29],[30]

Mechanism of integration

HIV integration phase is commenced on the completion of the Reverse transcription of viral DNA with the host cell. Beginning when the HIV DNA synthesis is complete, the HIV integrase enzyme must attach to the freshly synthesized DNA. The complexation of HIV integrase coupled with the HIV DNA lead to the formation of a complex, which we commonly term as intasome.

Initial theories proposed that integrase enzyme links with the end of the viral DNA in unique dimers, which further tend to fuse in order to form a tetrasomal structure. The integration process broadly takes place in 3 phases-

Phase 1- 3' ends processing

Integrate enzyme cleaves 2 nucleotides from the 3' ends of the HIV DNA, leading to the generation of 3'-OH (hydroxyl) groups on both the ends of the HIV DNA, which are much more reactive and in a dormant phase, prepares it to be inserted into the host cell.

Phase 2- Strand Transfer

This phase tends to start when the HIV DNA preliminarily docks into the host cell DNA. Integrate enzyme from the retrovirus cell happens to catalyse the HIV DNA insertion and transfer process into the host cell by the catalytic core of the integrase enzyme, which happens to be the most active and eminent component in the integration mechanism, which happens to launch a first multipronged

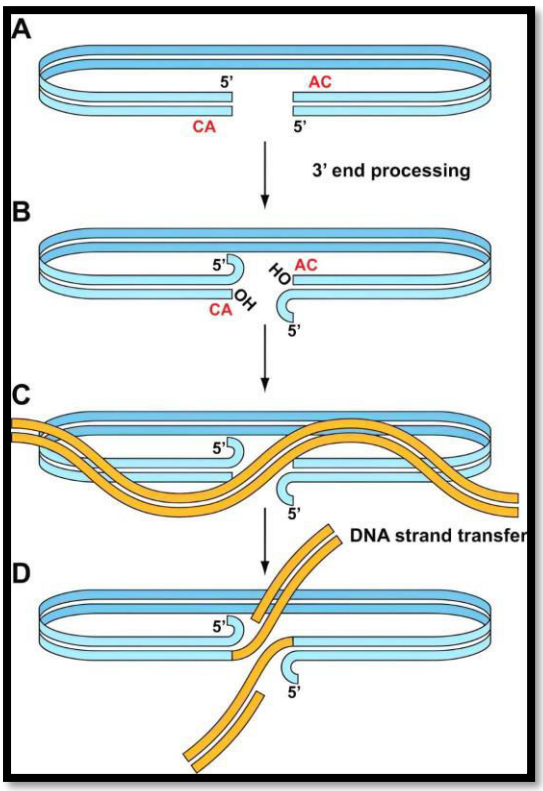

Fig (5): Two Essential Steps in HIV Integration[31]

attack by the hyper reactive 3'-OH first end of the HIV DNA on the host DNA strand parallel to the catalytic core of the HIV DNA integrase enzyme and the second attack on the other strand of the host DNA at an usual estimated length of about 4-6 base pairs farther from the viral genomic first 3' -OH conjugation with thehost cell.

These sequential conjugated attacks tend to cause the separation of both the strands of the host cell DNA from each other and furthermore intervening by addition of the viral DNA, causing the secretion of excess unused HIV integrase enzyme, finally leading to the formation of the host cell viral DNA hybrid.

Phase 3- Gap repair

The freshly obtained hybrid DNA straightens out, yet the remaining 4-6 base pairs of the host cell DNA substituted by the viral cells happens to have remained

attached to the host cell's DNA strand at the junction of strand transfer deeming these regions to be "DNA gaps". The enzymes released by the damaged host cell attempt to repair the DNA gaps by substituting with conjugational host nucleotides while other additional host enzymes try to smooth over the newly repaired DNA gaps as an imperative part of the DNA gap healing process[13].

On completion of the integration process, the viral genome is presently to be termed as provirus because it has turned to be a permanent irreplaceable part of the host DNA acting as a blueprint for the viral RNA transcription and protein synthesis facilitating persisted procreation.

This concludes the integration process by the formation of the host cell retrovirus hybrid formation and healing of all the DNA strand.

Structural elucidation of integrase (IN)

Integrase is a protein residing within the veal same, responsible for the insertion of the Viral DNA into the target cell. This antigen has some key notes to play in the entire lifecycle of HIV. Functionally, the IN enzyme is spur with a number of domains. which after partial proteolysis became more visible. As in previously studied specimens of HIV-IN, the specific domains were seen to be structurally distinguishable. That domain could make proteins of our qualitative interest.

The enzyme, Integrase (IN) contains an active site at the central domain and the core domain possesses poor solubility. But, upon significant change in an amino acid provided then and solubility[14].

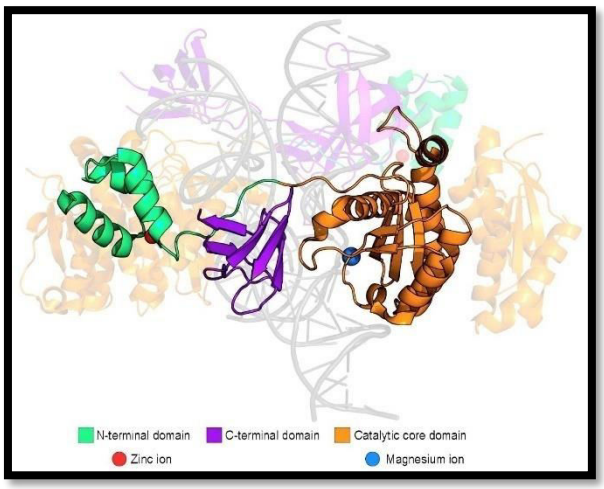

Fig (6): Integrase (IN)[32]

Making central core more prone to successful dissolution that enzyme can be helped to go under crystallization. Mutagenesis studies showed acidic residues, like D.D-35-E motif a potential region with three similar elements constituting a triad. After no longer the central region of the ASV Integrase (IN) was spotted, study revealed branch of enzymes forming the structural core of IN are from a nota superfamily comprises ofpoly nucleotidyl transterases which are counted under the banner of "RNaseA superfamily". Accompanying the isolation of catalytic domains, the aim was to be acquainted of the mechanism of interaction between the Integrase (IN) and the target DNA, by visualizing how does IN asses the positioning of active sites to assist the DINA strand transfer. Dimers of HIV and ASV-IN were derived often the crystallization of integrases fragments, which on proper analysis showed to contain exact stem dimer interfaces.

As the target DNA had sites of catalysis, having an exact distance of 5 nucleotides dissimilar to that of the IN dimers with oppositely situated active sites. Unfolding the structural framework of terminal domains of IN using Nuclear Magnetic Resonance (NMR).

1) **Amino Terminal Domain**: It got resolved being accompanied by Zn where the Zn2+ ions individually stabilized the bundles constituting amino terminal domain in accordance with the α–helics[15].
2) **Carboxy Terminal Domain**: In this terminal domain, after NMR spectroscopy, the carboxy terminal unveiled the association of β barrels resembling SH3.Eventually, resolving amino-terminal plus catalytic domain and catalytic domain plus carboxy-terminal, collectively called the two-domain structures had taken place, for a number of viral integrals.

   Such partial structures were no big help to elucidate the viral DNA and integrase (IN) connection. Through analysing those partial structures phased out mainly opaqueness and helped in procuring structures incorporating viral DNA ends and Integrase (IN) complex. Yet, they were irrelevant as the need of structures consisting of viral DNA was felt for proper modelling of active complexes, because of differential placements of the domain among a variety of partial structures. Taking a deep dive of research with Integrase (IN) obtained from Prototype Foamy Viruses (PFV) in combination with viral DNA made a landmark in the way to elucidate IN[16].

   Prototype Foamy Virus's intasome was made up with homotetramers (association of integrase upon viral DNA ends). This breakthrough provided a clear view on Integrase (IN) and viral DNA integration. The following tetramers provided by catalytic domain which further construct dimerization interface, initiate the formation of "dimer-of-dimers" architecture, that tetramer framework is not held with proteins only but the protein-DNA integrations confining a total area of 10,000 square Angstrom upon molecule[17].

   Prototype Foamy virus (PFV) ascertained the presence of divalent metal cations (Zn2+) on the Integrase (IN) active site. (F2D) Extending broader integrase, the PFV intasome had unfastened the blockage in understanding IN inhibitors function (ex-Raltegravir) like the obstruction of active sites and then dislocation of viral DNA 3' ends (disabling catalysis). The PFV IN structures share similarity to its kind of HIV-I, potentiating the clarification of the integrase inhibition action against retroviral proliferation by blocking IN[18].except, mild deviations the PEV IN can be of extensive use and utilising the resistance mutations map researchers are able to locate the mismatched regions among the following proteins (IN). This is why, the observation of actual HIV-Iintasome is well-sought.

Pre-integration phase

Prior to apprehending the integration phase, a chain of events occur which may ease the way for efficient uncovering and release of inner genetic material. A viral capsid protein (CA), confines the viral genetic components consisting of RNA, several proteins including Integrase (IN) & Reverse Transcriptase (RT) by forming a cage having the batch of enzymes within it. Interactive Capsid Proteins (CA) getting interconnected to each other seized the reason behind the viral structural and functional credibility[19],[20].

Making better use of the viral capsid, virologists are emerging a new method to counter and enrich the retroviral manifestation. There, the partial dissolution of CA is very crucial for kicking off reverse transcription and virologists are aiming at its disruption[21]. Underlining features of the CA assembly variably determine viruses ability to count. The outer capsid of the virus is made with different terminal domains namely, NTD and another CTD. These NTDs, CTDs are found to be linked with the help of linkers.

NTDs and CTDs being linked by adjustable linkers restructure into a large ring structure comprising approximately 5-6 protomers[20]. Eventually such goliath ring structures interlink with such same rings to create a cone resembling fullerene. That cone-like case is primarily composed of hexamers and pentamers where hexamers contribute to major parts, whereas, at the wide and narrow edges many monomers make up the space. Viral cone provides a nucleoprotein complex structure that acts as a basic model behind that alteration of shape which is occurred by the NTD-CTD intramolecular and intermolecular CTD-CTD interlinkage, inside the host cell's chromosomes.

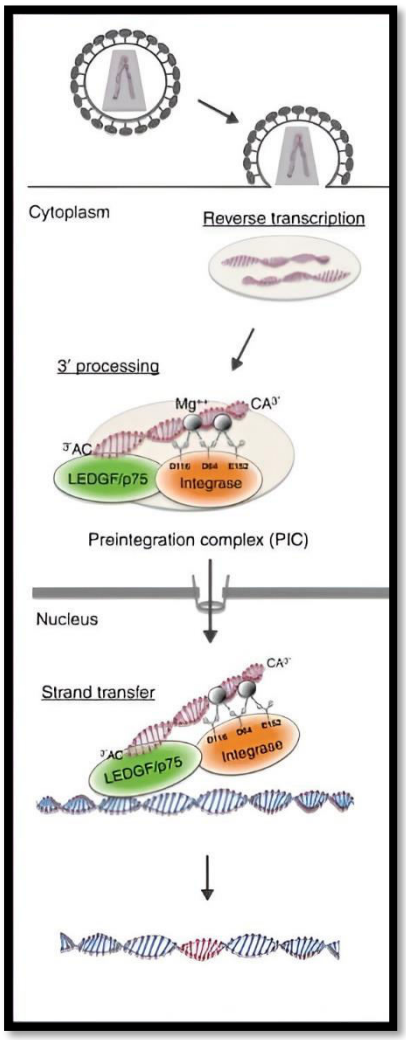

Fig (7): Formation of PICin the Integration process[33]

It was just the previous decade, when crystal structures bound drug - nucleic acid template got its spot; but any higher resolution structure of HIV-1 Reverse Transcriptase has garnered scientific attention since many years. Reverse Transcriptase of the HIV-1 retroviruses is made up of p66 and p51 subunits. However, the HIV-1 retrovirus's heterodimer sites that extensively participate in host's important cellular functions are cohabited with p66 subunit. Two such sites C- terminal RNase H and N- terminal RNA and DNA dependent DNA polymerase governed by p66 subunit incites the digestion of RNA-DNA hybrid forms. Consequently, liberation of polyphosphate and inclusion of nucleotides within growing DNA chain happen, so as in the time

of DNA polymerisation we can observe the conjunction of Mg2+ cation, catalytic residues of Asp 110, 185, 186. These operations come to be handy while decoding the potentiation of DNA 3'-OH assisting stabilisation of dNTP.

Factors affecting HIV integration

Numerous factors can be partially related to the occurrence of retroviral integration. Among them, plenty of host cell factors play pivotal roles in it and engage in the integration site selection procedures. Selectively to contain integration sites can also be analysed with this.

The following factors are essential for consideration -

1) **LEDGF/p75:** LEDGF in a co-activator, host cell protein mediating the DNA transcription and repair. The LEDGF/p75 is a procedure from the PSIP1 gene. Proving to be a potent mediator of integration as well as transcription efficiency, LEDGF/p75 became a sensation after it was ascertained to have a firm bond over IN protein of HIV.
2) **SRSF1:** This amino acid abundant splicing factor shows smooth interaction with the proteins and RNAs[22],[23].Many other factors belonging to this family are bound to show crucial regulation of splicing operations in the HIV-1[24],[25].
3) **Stimulatory Proteins:** A bunch of proteins such as BAF, HMGA, Ini - 1 assist the formation of PIC and they are intertwined with the DNA condensation, DNA coating.
4) **Cellular Chromatin Proteins:** In1, EED, SUV39H1, HP1 are associated with the heightened efficiency of integration.

Future perspective of HIV DNA integration

Deoxyribonucleic Acid (DNA) imprints a valuable mark in the way of HIV, infiltrating into host cells to begin their expedition through the integration process. But this valuable research piece holds the potential in the advancement as well as forms and builds superior understanding and countering the HIV infections.

i) Integration Site Mapping - Mapping onto the integration sites in infected cells forming a critical area to analyse for future purpose. The aim is to understand viral behaviour and there's risks on the function of infected cells. Integration sites inform the location where a viral DNA is inserted. The choosing of sites is not a normal or random method. After or during insertion various factors are observed like chromatin deformation, copying of host cells and interaction of both proteins present in viral and host body. Researchers gain some valuable information on how to summarise core preferences and how they should be executed which affect gene expression and cell identity.Integration can be inhibited with advanced targeted strategies in viral DNA, that minimize the total impaction on the host cells[26] and diminishes the risk chances of mutagenesis.

ii) Host Factor Identification - Viral integrase enzyme establishes the infection and concealed retroviruses via HIV integration into the host genome. This process is based on different factors that either support or restrict viral integration. With identification and recognition the host factors provide discernment into integrase mechanisms and prepare some opportunities for new therapeutic tactics.

An organized and good characterised host factor is LEDGF/p75, a chromatin binding protein influence in the integrase to transcription region that defines assurance safe and effective integration. But some drugs show blocking interest in viral integration like ALLINIs. Consequently inhibitory factors like APOBEC3 restrict HIV to form replicate. Modern methodology and structural biology have been coming under instrumentation in identifying these factors.

Furthermore, host factor studying in latency could inform strategies to eliminate concealed retroviruses.

iii) Investigation of Chromatin Structure - Chromatin, a complex product of DNA and proteins takes an active part in the determination of viral integrating sites with their structural features that regulate the viral gene expression. HIV integration is not randomly selected but also prefers a particular region where euchromatin activates for transcription on the genome. The dynamic nature makes chromatin a different DNA product than others by regulating histone modifications, DNA methylation and chromatin remodelers, directly impacts in the genomic region of the Pre-integration section. Research methodologies including ChIp-seq and ATAC-seq have been studied and taken under mapping integration sites into the chromatin section. A basic development of therapies is always aiming at the modification of chromatin complexes so that we can control HIV/AIDS positive patients by eliminating the infection[27].

Conclusion:

A host genome is captured by Human Immunodeficiency Virus(HIV) where it starts their life cycle through integration processes. Here, HIV allows to integrate Reverse - Transcribed DNA (provirus) into the reservoir cells, confirming the replication process and evasion of the human immune system. Viral integrase enzymes are very much impactful in the finding of special regions within viral genome participating in insertion stage.

Several significant implications are made by integration. First, it opens an opportunity to exploit in host cells for beginning viral transcription and production of fresh virions. After the integration, proviral products serve templates for viral RNA and proteins. Second thing is that, integration helps to form latent reservoirs where integration stands in non - active state. These kinds of reserve sections remain undetectable when we study in Antiretroviral therapy (ART). Moreover integration can damage host cell genetic expressions by their stability, potentiality, which is a big part in disease progression. Based in

integration sites, proviruses have the ability to impact nearby cell genes, including growth and immune response factors, sometimes creating complications like clonal expansion of infected cells.

We can simply conclude that we found out how HIV integrates into DNA strand and understand how this process informs the development of integrase inhibitors, a key to how to resolve the problem with modern advancements. However, elimination of latent reservoirs is a big challenge for us to achieve a complete healthcare situation in the country or globally. Don't forget that HIV can be treated with magnificent research into HIV integration mechanisms and variable therapeutic strategies.

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