



Fighting HIV-1 via Allosteric Integrase Inhibitors

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Abstract

AIDS as a world health problem caused by HIV-1 is described. Approaches for fighting HIV-1 are briefly mentioned with special emphasis on targeting integrase enzyme.

Keywords: Human immunodeficiency virus type 1; Integrase; Allosteric integrase inhibitors; Lens epithelium derived growth factor

Abbreviations: HIV-1: Human Immunodeficiency Virus Type 1; AIDS: Acquired Immunodeficiency Syndrome; RT: Reverse Transcriptase; PR: Protease; IN: Integrase; LEDGF/p75: Lens Epithelium Derived Growth Factor; SSC: Stable Synaptic Complex; FDA: Food and Drug Administration; PIC: Pre Integration Complex; ALLINIs: Allosteric Integrase Inhibitors.

Introduction

Human immunodeficiency virus type 1 (HIV-1) is a retrovirus that causes acquired immunodeficiency syndrome (AIDS) [1,2] if not treated. Since AIDS was reported for the first time in 1981 in a small number of patients [3-5] worldwide more than 25 million people have fallen victim to HIV infections but has developed into a major epidemic. HIV attacks the body's immune system, specifically the CD4 cells (T cells), which help the immune system fight off infections. Untreated, HIV reduces the number of CD4 cells (T cells) in the body, making the person more likely to get other infections or infection-related cancers. Over time, HIV can destroy so many of these cells that the body can't fight off infections and

disease. The most common approach for fighting HIV-1 requires critical knowledge of the key enzymes that dominate the viral replication cycle. Research efforts identified HIV-1 reverse transcriptase (RT), protease (PR), and integrase (IN) as essential enzymes for viral replication cycle. Consequently, drug discovery researcher's effort for fighting HIV-1 has been focused on designing and synthesizing novel molecules that act as inhibitors to such enzymes. Such drug has transformed the prognosis of an HIV-1 infection from a once deadly illness to a chronic, manageable disease by preventing progression to AIDS [6].

Discussion

HIV-1 integrase (IN) is one of three essential enzymes for viral replication and the focus of drug discovery and development efforts. HIV-1 IN exists in various forms, from monomer to higher-order multimers, in solution. It is responsible for integration of the viral DNA reverse transcriptase into cellular chromatin through two chemical reactions 3' processing (cytoplasm) and DNA strand transfer (nucleus). During the early stage of HIV-1 replication, a tetramer of IN assembles with reverse

transcribed viral DNA ends to form the stable synaptic complex (SSC) or intasome in the cell cytoplasm. The

intasome contains a tetramer of IN, with two inner subunits directly engaging the viral DNA ends (Figure 1).

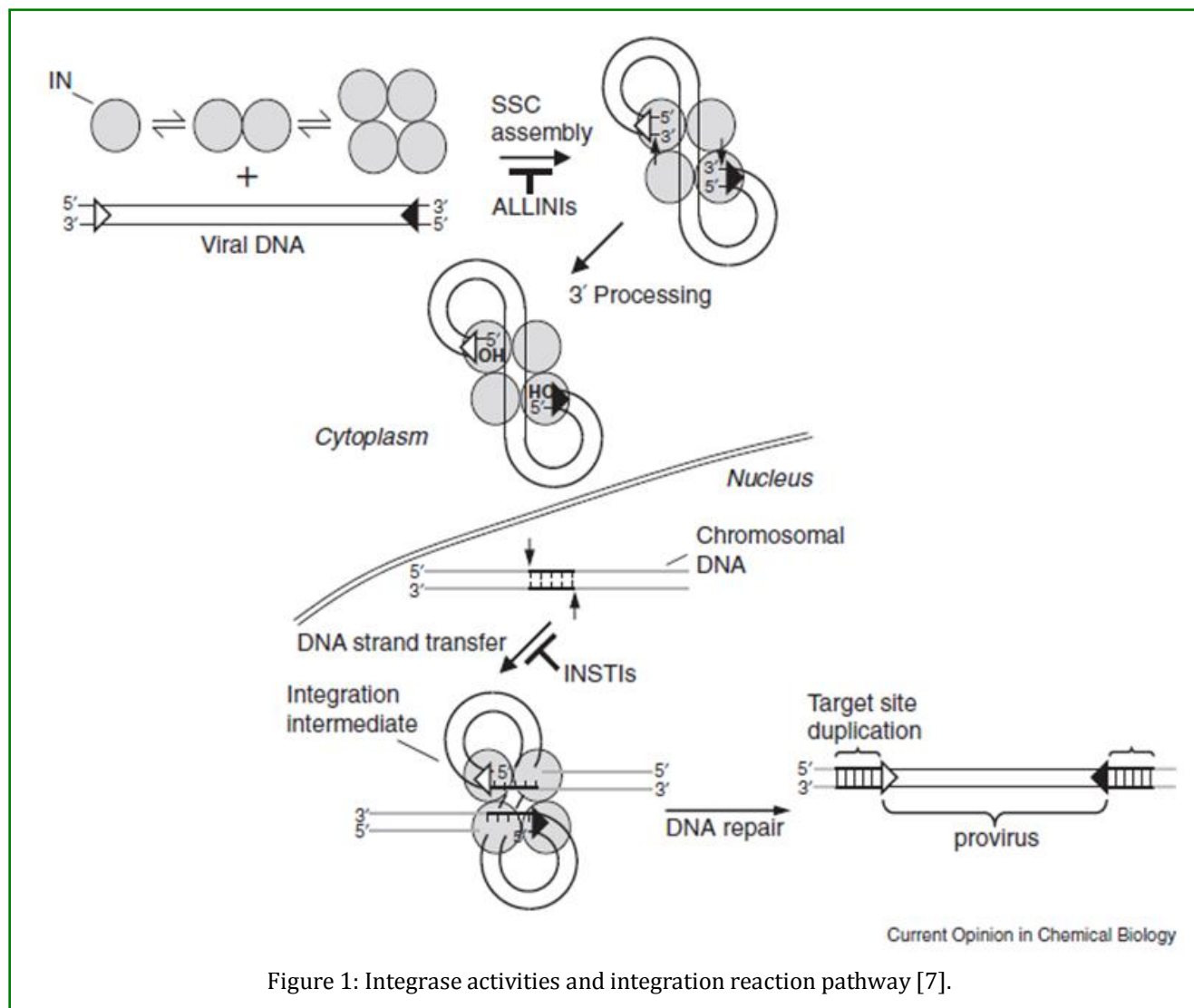


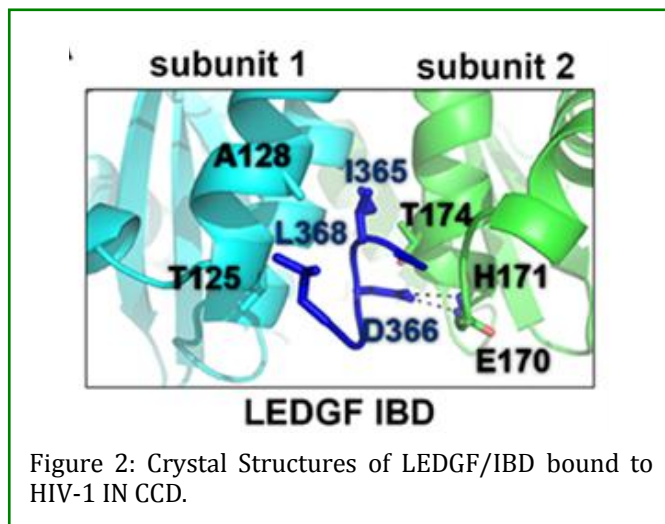
Figure 1: Integrase activities and integration reaction pathway [7].

In recent years it has been recognized as an attractive target for HIV therapy. Raltegravir was the first Food and Drug Administration (FDA) approved integrase inhibitor, although resistance to this drug in the clinic has been observed. Second generation integrase inhibitors, including elvitegravir and dolutegravir have been developed, but all of these compounds target the active site of the enzyme. The HIV-1 is characterized by a high turnover and mutation rate which leads to resistant to this drug in the clinic. The new approaches are targeting the protein-protein interactions between the HIV-1 integrase and its cellular cofactor Lens epithelium derived growth factor (LEDGF/p75), has increasingly gained attention as a valuable target for a new active compounds.

The cellular chromatin associated protein LEDGF/p75 (key binding partner) binds the HIV-1 integrase tetramer and navigates the pre integration complex (PIC), which also contains additional viral and cellular proteins, to active genes during integration. The integration is facilitated by cellular chromatin-associated protein LEDGF/p75, which tethers the lentiviral intasomes to active genes [8].

A Synthesis of small molecules mimic the co-cellular factor, bind at the integrase dimer interface and disrupt the binding of LEDGF/p75, production IN tetramer form (active form) as well as promoting aberrant higher order protein oligomerization (IN multimerization). In 2005 the

crystal structure of IBD in complex with a dimer of the integrase catalytic core domain was reported (Figure 2), by Cherepanov et al. [9] identifying the amino acid residues of LEDGF/p75 mediating the interaction with IN.



The key interactions between LEDGF/p75 and IN-CCD domain include a bidentate hydrogen bond between aspartate-366 (D366) on the LEDGF/p75 IBD and glutamate-170 (E170) and histidine-171 (H171) residues on one IN subunit. In addition, isoleucine-365 (I365) of the IBD resides in a hydrophobic pocket containing residues leucine-102 (L102), alanine-128 (A128), and tryptophan-132 (W132) on the second subunit of the IN-CCD. Recently 2-(quinolone-3-yl) acetic acid derivatives identified as Allosteric integrase inhibitors (ALLINIs) and used for elucidation the biological and mechanistic activity of ALLINIs as multifunctional compounds. A128T mutation in integrase has been marked as a resistance to the quinolone scaffold. So the medicinal chemists used the previous studies to synthesize new compounds with certain criteria enhance the potency of ALLINIs, increase the selectivity for promoting allosteric IN multimerization and overcome the resistance escape mutations.

Recently, in 2016, as part of research efforts toward novel allosteric HIV-1 integrase inhibitors a cooperative two reports [10,11] including researchers from Ohio State University and Helwan University have been published. In the first report [10], the authors developed indole -based allosteric inhibitors of HIV-1 integrase which bind to IN dimer interface at the LEDGF/p75 binding pocket and exhibit a multimodal mechanism of action. The fused five-membered indolering, however, allow this class of compounds to avoid steric and electrostatic repulsions by the A128T mutation that leads to marked resistance to many quinoline-based ALLINIs. Additionally, the synthetic

versatility of indole core provides numerous opportunities for functionalization and structural manipulation in the development of analogues. The second report [11] has shown that the atomic models constructed based on the concept that ALLINIs binding at the CCD dimer interface which lead to aberrant multimerization are able to provide physical explanations for a number of key experimental results concerning the multimerization including the exceptional potency in both quinoline and pyridine based ALLINIs. It also sheds light on the mechanism of action of the allosteric inhibitors of HIV-1 IN and provides insights into the design of more potent compounds.

Conclusion

On conclusion resistance to anti HIV-1 drugs have always been and still emotive for research efforts towards novel anti HIV-1 drugs.

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