HIV LIFE CYCLE: TARGETS FOR ANTI-HIV AGENTS

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1.1 INTRODUCTION: OVERVIEW OF HIV LIFE CYCLE

The life cycle of human immunodeficiency virus (HIV) encompasses several crucial steps which can be considered as targets for chemotherapeutic intervention (Fig. 1.1). The life cycle starts with adsorption of virions (virus particles) to the host cell, where the viral envelope glycoprotein gp120 interacts, first, nonspecifically, with heparan sulfate; second, specifically, with the CD4 (cluster of differentiation 4) receptor; and, third, specifically, with the coreceptor CXCR4 or CCR5. Like other enveloped viruses, HIV enters the cell by fusion between the viral envelope and the cellular plasma membrane: for HIV; this process is mediated by the viral glycoprotein gp41 and allows the penetration of the nucleocapsid into the cell. After the viral RNA (ribonucleic acid) genome has been freed from its capsid through an ill-characterized process termed decapsidation (or uncoating), the viral (+)RNA is converted into proviral double-stranded (ds, ±)DNA (deoxyribonucleic acid) through the virion-associated reverse transcriptase. This genomic viral DNA is then integrated into the host cell genome through HIV integrase (like reverse transcriptase, a virion-associated enzyme). Being an integral part of the host genome the proviral DNA is subject to the normal transcription and translation machinery of the cell for expression of its genes, although for HIV this is additionally regulated by specifically induced viral regulatory proteins such as Tat (transcription trans activator) and Rev (regulator of expression of viral proteins). Viral RNA and proteins will then assemble at the cell membrane to produce progeny virus particles that are released through the process termed budding. Following translation of the viral precursor proteins pp55 gag and pp160 gag–pol, the viral protease (which is autocatalytically cleaved) will cleave these precursor proteins into the structural (gag) proteins [MA (matrix antigen) p17, CA (capsid antigen) p24, NC (nucleocapsid) p7] and functional (pol) proteins [PR (protease) p11/p11, RT (reverse transcriptase) p66/p51, IN (integrase) p32 tetramer]. This proteolytic processing is inherent to the production of infectious progeny virions, and, while coinciding with the assembly of the new virus particles, it may continue after the budding has taken place.

1.2 VIRUS ADSORPTION: INTERACTION OF HIV WITH CD4 RECEPTOR

Before HIV finds its specific receptor CD4, it first interacts nonspecifically with heparan sulfate, which is widely
expression on animal cells and involved in virus–cell binding of a broad array of enveloped viruses, including herpes simplex virus and Dengue virus. Numerous polyanionic substances (i.e., polysulfates, polysulfonates, polycarboxylates, polynucleotides, polyoxometalates, and negatively charged albumins) have been shown to inhibit HIV replication by preventing virus adsorption to the surface of the host cells, but none of these substances have yet found their way to a clinical application, whether systemic or topical.

The specific interaction of HIV with CD4, a marker for HIV-sensitive host cells, is considered a much more specific target for potential therapeutic intervention. CD4 is an integral membrane glycoprotein, belonging to the immunoglobulin gene superfamily, that is expressed mainly on the surface of T lymphocytes and cells of the macrophage/megakaryocyte lineage. It consists of an extracellular region of 370-amino-acid residues organized in four domains (D1–D4), a hydrophobic membrane-spanning region of 25 amino acids, and a highly charged cytoplasmic tail of 38 amino acids. The D1 loop has been identified as the primary binding site for the HIV envelope protein gp120. Of particular importance for the binding of gp120 are the positively charged amino acid residues at positions 46 and 59 surrounding the phenylalanine residue at position 43 (denoted as the Phe 43 cavity) (Fig. 1.2).

Various analogues of cyclotriazadisulfonamide (CADA, or 9-benzyl-3-methylene-1,5-di-p-toluenesulfonyl-1,5,9-triazacyclododecane) (Fig. 1.3) have been found to specifically downmodulate the expression of CD4 without altering the expression of any other cell receptor examined, including HIV coreceptors, and a close correlation was found between the anti-HIV potency of the CADA analogues and their ability to downmodulate the CD4 receptor. The potential of CADA and its analogues in the treatment of HIV infections and, possibly, other diseases (whether infectious or immunological) that are mediated by CD4 needs to be further explored.

### 1.3 PRELUDE TO FUSION: INTERACTION OF HIV WITH CXCR4 OR CCR5 CORECEPTOR

Following its interaction with the CD4 receptor, the viral envelope gp120 must interact with its coreceptor, CXCR4 (C–X–C chemokine receptor 4) for T-tropic or X4 HIV strains or CCR5 (C–C chemokine receptor 5) for M-tropic or R5 HIV strains. CXCR4 and CCR5 normally act as the receptors for the C–X–C chemokine SDF1 (stromal cell-derived factor 1) and the C–C chemokines RANTES (regulated upon activation, normal T cell expressed and secreted) and MIP-1 (macrophage inflammatory protein 1), respectively. The coincidental use of CXCR4 and CCR5 by HIV as coreceptors to enter cells has prompted the search for CXCR4 and CCR5 antagonists, which, through blockade of
the corresponding coreceptor, might be able to block HIV entry into the cells (Fig. 1.4).

The best characterized of the CXCR4 antagonists is AMD3100 (previously called JM3100)\(^\text{10}\) (Fig. 1.5). It was originally discovered as an anti-HIV agent with strong inhibitory effect on the replication of X4 HIV strains\(^\text{11}\) and was later found to inhibit X4 HIV replication by a selective antagonization of CXCR4\(^\text{12}\) then found to specifically mobilize hematopoietic stem CD34\(^+\) cells from the bone marrow into the bloodstream (by interruption of the interaction of CXCR4 with its normal ligand SDF1, which is responsible for the “homing” of the stem cells in the bone marrow).

The most advanced among the CCR5 antagonists is maraviroc\(^\text{13}\) (Fig. 1.5), which has been approved for clinical use in the treatment of HIV infection. Limitation in the clinical use of maraviroc is that it is only effective against CCR5-using R5 HIV-1 strains. From dual (CCR5 and CXCR4)-tropic or mixed HIV populations that use both CCR5 and CXCR4 (which are common among highly treatment experienced patients), maraviroc may select for the outgrowth of pure CXCR4-tropic X4 strains.\(^\text{14}\) In addition, R5 HIV-1 strains may develop resistance to maraviroc while still utilizing the inhibitor-bound receptor for entry.\(^\text{15}\) Obviously, to cope with dual-tropic or mixed X4/R5 HIV-1 populations, a combination of CXCR4 inhibitors with CCR5 inhibitors will be ultimately needed.

\subsection*{1.4 VIRUS–CELL FUSION: SIX-HELICAL BUNDLE FORMATION AND INSERTION OF FUSION PEPTIDE INTO CELL MEMBRANE}

While the viral glycoprotein gp120 is responsible for virus interaction with the CD4 receptor and CCR5 or CXCR4 coreceptor, the viral gp41 glycoprotein (which has remained noncovalently attached to gp120 after their precursor glycoprotein gp160 has been cleaved by cellular proteases to yield the gp120/gp41 heterodimer) is responsible for the fusion of the viral envelope with the cell membrane. The gp41 glycoprotein contains four major functional domains, starting from the N-terminus toward the C-terminus: (i) the fusion peptide, (ii) heptad repeat 1 (HR1), (iii) heptad repeat 2 (HR2), and (iv) the transmembrane domain that anchors gp41 into the viral lipid bilayer. When the N-terminal fusion peptide of gp41 is inserted into the host...
cell membrane, the three HR2 domains of the gp41 trimer loop back in a triple hairpin and “zip” themselves into three highly conserved hydrophobic grooves on the outer face of the HR1 trimeric bundle. This conformational change results in the formation of a six-helical bundle which pulls the outer membranes of both virus and cell into close physical proximity, thus enabling the two membranes to fuse (Fig. 1.6).

Enfuvirtide (originally designated DP-178, pentafuside, or T-20) (Fig. 1.7) is homologous to part of the HR2 region, and, while T-20 will itself engage in a coiled-coil interaction with HR1, it prevents the six-helical bundle formation required to initiate the fusion process. Enfuvirtide (Fuzeon®, the only HIV drug injected subcutaneously, is generally used in combination with HAART (highly active antiretroviral therapy) regimens. Even if added onto highly active four-drug regimens, enfuvirtide has still proved able to afford only an incremental benefit. However, enfuvirtide has a low genetic barrier to resistance with mutations primarily arising in the HR1 domain. This low genetic barrier to resistance underscores the importance of combining enfuvirtide with other anti-HIV agents.

Figure 1.4 Coreceptor (CXCR4 or CCR5) antagonists. During the viral adsorption process, (a) the viral envelope glycoprotein gp120 interacts with the CD4 receptor at the cell membrane; (b) subsequently, gp120 interacts with the coreceptor CXCR4 for T-tropic (X4) HIV strains or CCR5 for M-tropic (R5) HIV strains, whereupon (c) the viral glycoprotein gp41 anchors into the cell membrane. CXCR4 and CCR5 antagonists bind to CXCR4 or CCR5 and thus block their interaction with HIV gp120. (Data from De Clercq.10)

Figure 1.5 Structures of AMD3100 (Mozobil) and UK-427857 (Maraviroc).
1.5 FROM VIRAL RNA TO PROVIRAL DNA: REVERSE TRANSCRIPTION

To convert the genomic viral RNA to pregenomic proviral DNA, three successive enzymatic reactions, all ensured by the p66 subunit of the p66/p51 RT (reverse transcriptase) heterodimer, are required: (i) transcription of the (+)RNA strand to a (−)DNA strain, which, being complementary to the (+)RNA, remains hybridized with its template; (ii) degradation of the (+)RNA strand of the (−)DNA−(+)-RNA hybrid by the p15 [RNaseH (H for hybrid)] subdomain of p66; and (iii) formation of the (+)DNA strand from the

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**Figure 1.6** Binding of gp120 to the coreceptor triggers conformational changes in gp41, including the formation of a triple-stranded coiled coil with insertion of the fusion peptide into the cell membrane. The transition from the triple-stranded coiled coil to the six-helical bundle conformation is the proximal cause of fusion between the viral envelope and cell membrane and is inhibited by T20 (enfuvirtide). (From Doms.16)

**Figure 1.7** Structure of enfuvirtide (DP-178, pentafuside, T20).
DNA template, thus producing a (±)DNA duplex. Both functions (i) and (ii) are catalyzed by reverse transcriptase, the catalytic site being located in the palm domain (Fig. 1.8), which contains a substrate [deoxyribonucleotide triphosphate (dNTP)] binding site (indicated by the dot in Fig. 1.8) and an allosteric site (indicated by the asterisk in Fig. 1.8) at about 15 (1.5 nm) distance from the catalytic site. Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs, NtRTIs) are targeted to the catalytic (dNTP binding) site, whereas the nonnucleoside reverse transcriptase inhibitors (NNRTIs) are targeted to the allosteric (NNRTI binding) site.

To interact with their target sites, the NRTIs [i.e., zidovudine (Retrovir®), didanosine (Videx®), zalcitabine (Hivid®), stavudine (Zerit®), lamivudine (Epivir®), abacavir (Ziagen®), and emtricitabine (Emtriva®)] and NtRTIs [i.e., tenofovir (marketed as tenofovir disoproxil fumarate, Viread®)] must first be phosphorylated to their triphosphate derivatives (NRTI triphosphates) or diphosphate derivatives (NtRTI diphosphates), which can be readily accomplished by two or three consecutive intracellular phosphorylations. NNRTIs [i.e., nevirapine (Viramune®), delavirdine (Recriptor®), efavirenz (Sustiva®, Stocrin®)] do not need any intracellular metabolism and are able to interact as such with their target site. RT has proven to be the favored target enzyme for drug development against HIV infection (AIDS). In addition to those that have been mentioned (Fig. 1.9) (and which have all been approved for the treatment of AIDS), several other NRTIs (i.e., apicitabine, amdoxovir, Racivir®, Reverset®) and NNRTIs (i.e., etravirine, rilpivirine, dapivirine) are in clinical development. These and yet other NRTIs, NtRTIs, or NNRTIs may join the anti-HIV drug armamentarium in the (near) future.22,23

1.6 INTEGRATION OF PROVIRAL DNA INTO HOST CELL GENOME BY HIV INTEGRASE

Approximately 40–100 integrase molecules are packaged within each HIV particle.24 The primary role of integrase is to catalyze the insertion of the proviral DNA into the genome of infected cells. Integration is required for viral replication because efficient transcription of the viral genome and production of viral proteins require that the proviral DNA is fully integrated into the cellular genome. Following reverse transcription, the proviral DNA is primed for integration by integrase-mediated 3' processing, which corresponds to an endonucleolytic cleavage of the 3' ends of the proviral DNA, thereby generating CA-3'-hydroxyl ends (Fig. 1.10). Following 3' processing, integrase remains bound to the proviral DNA as a multimeric complex that bridges both ends of the viral DNA within intracellular particles termed PICs (preintegration complexes). PICs are able to cross the nuclear membrane. Once in the nucleus, the integrase catalyzes the insertion of the proviral DNA into the host chromosome by a strand transfer reaction, consisting of the ligation of the viral 3'-OH DNA ends (generated by 3' processing) to the 5'-phosphates of host chromosomal DNA. Completion of integration can only take place after trimming of the last two nucleotides at the proviral DNA 5' ends and extension (gap filling from the 3'-OH ends of the genomic DNA).24

Among the furthest advanced integrase inhibitors in clinical development are MK-0518 (raltegravir) and GS-9137 (elvitegravir) (Fig. 1.11). Raltegravir has been approved by the U.S. Food and Drug Administration (FDA) in 2007 and elvitegravir’s approval is pending. Both compounds inhibit the strand transfer reaction in the integration process (Fig. 1.10) and were validated as genuine HIV

Figure 1.8 Three-dimensional structure of HIV-1 reverse transcriptase with the fingers, palm, thumb, connection, and RNaseH domains, all belonging to the p66 subunit and the p51 subunit. (From Tantillo et al.21 with modifications.)
Clinical studies have indicated that both raltegravir and elvitegravir upon 10-day monotherapy can achieve $2 \log_{10}$ reductions in viral load. When added onto an optimized background regimen, raltegravir, at all three doses tested (200, 400, or 600 mg orally twice daily), offered better viral suppression than placebo over a 24-week treatment period. Clearly, the integrase inhibitors (INIs) may be welcomed [following the NtRTIs, NNRTIs, Protease inhibitors (PIs), and virus entry inhibitors] as the next new class of anti-HIV drugs. As for all other classes of HIV inhibitors, INIs should be used in combination drug regimens and carefully monitored for the emergence of drug-resistant virus strains.

The regulation of transcription of HIV is an extremely complex process requiring the cooperative action of both viral and cellular components. In latently infected resting CD4$^+$ T cells, HIV transcription seems to be repressed by deacetylation events mediated by histone deacetylases (HDACs). Upon reactivation of HIV from latency, HDACs are displaced in response to the recruitment of histone acetyltransferases (HATs) by nuclear factor κB (NF-κB) or the viral transcriptional activator Tat, and this results in multiple acetylation events. Following chromatin...
remodeling of the viral promoter region, transcription is initiated. The complex of Tat with p-TEFb then binds to the TAR (Tat response) element, thereby positioning CDK9 to phosphorylate the cellular RNA polymerase and thus ensuring transcription elongation. Other phosphorylation and acetylation events accompany and may at least partially account for the (activation of the) HIV transcription process (Fig. 1.12).

Numerous inhibitors of the HIV transcription process have been described. They may be targeted at the stages of NF-κB activation (e.g., α-tocopherol, coumarins, acridone derivatives, iron chelators), NF-κB binding (pyridine N-oxide derivatives), the NF-κB signaling pathway (cepharanthine, carboxyamidotriazole), p-TEFb (flavopiridol, roscovitine), p300/CREB (curcumin), or, most interestingly, the Tat–TAR interaction (CGP64222, Tat peptide mimetics, quinolone derivatives, arginine–aminoglycoside conjugates RNA aptamers, and TAR RNA decoys). Although these HIV transcription inhibitors may be expected to prevent HIV gene expression in both acute and chronic, as well as
latent, infected cells, none of these therapeutic options has been pursued clinically.

1.8 PROTEOLYTIC CLEAVAGE OF PRECURSOR INTO MATURE VIRAL PROTEINS

To be converted to the mature Gag (p17, p24, p7) and Pol (p11/p11, p66/p51, and p32) proteins, the precursor Gag and Gag–Pol proteins have to be cleaved at specific peptide linkages by the HIV protease (p11/p11) after this enzyme itself has been cleaved auto-catalytically from the Gag–Pol precursor protein. If this proteolytic cleavage is blocked, that is, by PIs, no infectious particles will be produced, and virus spread will be halted. At present, 10 PIs have been approved: saquinavir (Invirase®, Fortovase®), ritonavir (Norvir®), indinavir (Crixivan®), nelfinavir (Viracept®), amprenavir (Agenerase®, Prozei®), lopinavir (combined with ritonavir at 4/1 ratio, Kaletra®), atazanavir (Reyataz®), fosamprenavir (Lexiva®, Telzir®), tipranavir (Aptivus®), and darunavir (Prezista®). The development of an eleventh PI, brecanavir, was recently discontinued because of "formulation" problems.

Except for tipranavir (which is based on the coumarin lactone scaffold), all available protease inhibitors can be considered as peptidomimetic (Fig. 1.13). They are built upon an hydroxyethylene motif, which mimics the peptide linkage. Whereas the peptide linkage can be readily hydrolyzed by the HIV protease, the hydroxyethylene bond cannot. The surrounding parts of the protease inhibitor are very much similar to the amino acid residues around the peptide linkage that is cleaved in the normal substrate, so the HIV protease is "fooled" and, if it were, imprisoned by its "funny" substrate, the protease inhibitor. Recently, it has been demonstrated that some protease inhibitors, that is, darunavir and tipranavir, may also block dimerization at its nascent stage of protease.30

The structures of tipranavir and darunavir, the last PI to be licensed for clinical use, are depicted in Fig. 1.14. Darunavir has, akin to the other PIs, proven efficacious in the treatment of HIV infections when used as an integral part of drug combination therapy.31 As was first demonstrated with lopinavir, and now is customary for all PIs, ritonavir is added onto a therapeutic PI-containing regime just to "boost" its activity. Ritonavir-boosted tipranavir has proved more efficacious than other ritonavir-boosted protease inhibitors following a 24-week treatment period.32,33 In lopinavir-naïve, treatment-experienced patients, darunavir–ritonavir was noninferior to lopinavir–ritonavir treatment from a virological viewpoint and may therefore be considered as a treatment option for this population.34

1.9 VIRAL CAPSID FORMATION: ULTIMATE STEP TO BLOCK VIRUS PRODUCTION?

A very late and perhaps the ultimate step in the HIV life cycle that could serve as target for therapeutic intervention involves the conversion of the capsid precursor p25 (CA-SP1) to mature capsid protein p24 (CA), which depends on CA-SP1 cleavage (Fig. 1.15).35 This CA-SP1 cleavage can be blocked by bevirimat [3-O-(3',3'-dimethylsuccinyl)butyrolinic acid (PA-457)] (Fig. 1.16).36 Virions generated in the presence of bevirimat exhibit aberrant capsid morphology and are no longer infectious. Resistance mutations to bevirimat have been localized near the CA-SP1 cleavage site (Fig. 1.15).35 As bevirimat is the first-in-class HIV maturation inhibitor and, therefore, represents a new assault on HIV, in vivo efficacy data are eagerly awaited (http://www.panacos.com/product_2.htm). Bevirimat is well absorbed after oral administration and its half-life is unexpectedly long (60–80 h),37 which may facilitate infrequent, that is, twice-weekly, dosing.

1.10 CONCLUSION: COMBINATION THERAPY

With the advent of the integrase inhibitors (INIs), following the NRTIs, NtRTIs, NNRTIs, PIs, and FIs (and other viral
Figure 1.12 Model for regulation of Tat-mediated transcription. Initially, nonacetylated Tat interacts with P/CAF which was found to be associated with the HIV-1 promoter only in response to Tat. P/CAF acetylates Tat at position Lys28. This subsequently abrogates the interaction between P/CAF and Tat but significantly enhances its interaction with p-TEFb, which is released from its association with MAQ1/HEXIM1 and 7SK snRNA upon different stimuli, including stress, ultraviolet light, DRB, and hypertrophic signals. The complex of Tat with autophosphorylated p-TEFb then binds the upper bulge and loop structures of TAR, thereby positioning CDK9 to phosphorylate also the negative elongation factors NELF and DSIF, which repress transcription by binding to the lower stem in TAR, as well as the CTD of RNAPII on both Ser2 and Ser5. These phosphorylation events result in the release of the transcriptional elongation block. In addition to the productive elongation mediated by the hyperphosphorylated RNAPII, Tat becomes acetylated by p300/CBP on Lys50, resulting in the dissociation of TEFB-Tat from TAR RNA and subsequent binding to the elongating RNAPII. Furthermore the acetylation of Tat on Lys50 serves as a signal to recruit P/CAF generating a p-TEFB-Tat-P/CAF ternary complex associated with RNAPII during transcriptional elongation. (Data from Stevens et al.29)

Figure 1.13 Currently available PIs (protease inhibitors) except for tipranavir act as peptidomimetic inhibitors in that they are built upon an hydroethylene scaffold which mimics the peptidic linkage in the normal substrate but cannot be hydrolyzed by the protease.
entry inhibitors), the sixth class of anti-HIV agents has become available for clinical use in the treatment of HIV infections (AIDS). Starting from these different classes of anti-HIV drugs, numerous drug combinations could be conceived, containing multiple (two, three, four, five, or even six) drugs (Fig. 1.17). The increasing availability of new anti-HIV drugs has, on the one hand, increased the number of options, while, on the other hand, made the right choice more difficult.

Over the past decade HAART has gradually evolved from drug regimens with more than 20 pills daily (i.e., stavudine plus lamivudine plus indinavir) in 1996 to 3 pills daily [i.e., zidovudine/lamivudine (Combivir®) twice daily and efavirenz once daily] in 2003 to 2 pills daily [i.e., emtricitabine/tenofovir disoproxil fumarate (Truvada®) and efavirenz] in 2004 and finally to one pill daily in 2006 (Atripla®, containing tenofovir disoproxil fumarate plus emtricitabine and efavirenz).

The triple-drug combination tenofovir disoproxil fumarate (TDF), emtricitabine [(-)FTC], and efavirenz has proved more efficacious (in terms of virological and immunological response) and is less prone to toxic side effects than the other arm of the study (GS934), consisting of combivir (zidovudine/lamivudine) and efavirenz, over a period of 48, 96, and recently extended to 144 weeks. The first study to assess the use of the NNRTI etravirine with the PI darunavir (boosted by ritonavir) in HIV-1-infected subjects with no treatment options showed impressive virological responses (HIV RNA reduction of 2.7 log_{10} copies per milliliter) over a 24-week treatment period. This underscores the high and as yet hardly explored potential of combinations of NNRTIs with PIs in the treatment of HIV infections.
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