Chapter 5
The Progress of New Targets of Anti-HIV and Its Inhibitors

Ke Z. Wu and Ai X. Li

Abstract HIV-1 virus is the largest genetic variation in human pathogens, with a high reproduction, high mutation, and high reorganization. At present, commonly prescribed drugs of anti-AIDS mainly contain nucleoside analogue reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, protease inhibitor, and integrase inhibitor. With rapid development in biotechnology during the latest decades, it has gradually uncovered not only the details of fusion and endocytosis between HIV and the host cells but also the necessary enzymes of HIV-1 during the whole life cycle, which brings about great progress in the field of anti-AIDS drugs development. In this article, we focus on some crucial proteins and cofactors correlated with the virus or the human defense function. The cofactor CCR5 and the viral envelope protein gp120 are significant in the initial process of fusion between HIV-1 and the host cells. Both of them become important targets of anti-HIV, and numerous inhibitors have been developed in which some have entered various stages of clinical trials or even been approved for marketing. Besides, the target of virus infectivity factor (Vif) and TRIM5-α protein is correlating with the host defense system. The inhibition of the former and the expression of the latter will increase the ability of response to the viral invasion. Both of them are still at the experimental stage. New targets and some corresponding inhibitors have been referred in this review; it is hoped that it can provide some clues for the drug development of anti-HIV.

Keywords Anti-HIV • Targets • Inhibitors

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5.1 Introduction

Acquired immune deficiency syndrome (AIDS), caused by human immunodeficiency virus (HIV), is a worldwide serious infectious disease. Up to the end of 2013, there have been 78,000,000 HIV patients over the world, and more than 3,900,000 people have died from AIDS. Heretofore, 26 anti-HIV drugs have been approved by FDA mainly distributing in six targets with different mechanisms including those well-known zidovudine and indinavir (Rower et al. 2012; Geng et al. 2010). Belonging to a reverse transcription virus, the viral nucleic acid is RNA and is enclosed by protein capsid in cubical symmetry which then recognizes the membrane of the host cell. This virus has no necessary genetic materials from the human body for its reproduction (Hollox and Hoh 2014). The biotechnology, rapidly developing during the latest decades, has gradually uncovered not only the details of fusion and endocytosis between HIV and the host cells but also the necessary enzymes of HIV during the whole life cycle that brings about great progress in the field of anti-AIDS drugs development then. Normally, according to the mechanism of infection process, the targets of anti-HIV can be divided into protease, reverse transcriptase, integrase, and so on. Unfortunately, during the drug therapy (highly active antiretroviral therapy, HAART) for AIDS, more and more drug-resistant virus emerge, and many HIV sufferers have to face the embarrassment of no cure for certain conditions. Therefore, searching for new targets and developing effective inhibitors of anti-AIDS have practical significance now.

Through overall documents consulting, this article mainly concerned about the new targets and corresponding inhibitors in recent years which aim to raise rational drug therapy strategies of anti-AIDS.

5.2 Research Situation

5.2.1 The Target CCR5 and Its Inhibitors

CC chemokine receptor 5 (CCR5) (Fig. 5.1), one of the coreceptors of HIV-1, is a new target of anti-HIV therapy (Lucia 2010). Experiments have shown that HIV-1 infects the human body by combining with the CD4 cell which is one of the most important immune cells in the human immune system. But subsequent studies have also found that the invasion of HIV-1 will not be successful only mediated by the CD4 cells, and one or more coreceptors are necessary during the initial process. Thus, a series of coreceptors of HIV-1 including CXCR4, CCR5, and integrin α4β7 have been discovered in laboratory (Aiamkitsumrit et al. 2014). As members of G protein-coupled receptors (GPCR) superfamily, CCR5 is analogous in the structural features to most other chemokine receptors which are essentially composed of seven transmembrane regions and three extracellular loops (Tan et al. 2013). From the view of pathology, the interaction between gp120 and CCR5 can be

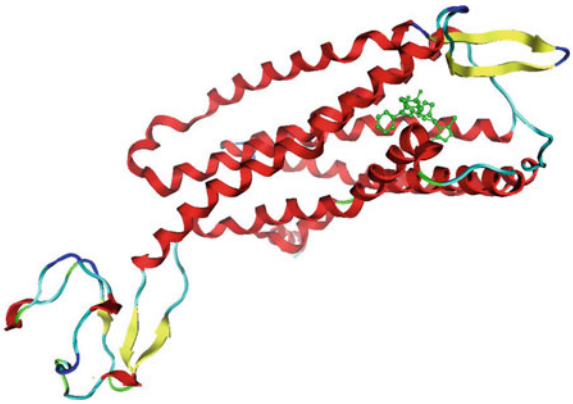

Fig. 5.1 CC chemokine receptor 5 (slab *ribbon*) and its inhibitor maraviroc (*green*)

divided into two steps. Firstly, the N-terminal region of CCR5 recognizes and combines with gp120 in a rational conformation. Secondly, as result of the conformation change of the two molecules, the interaction between the extracellular loops of CCR5 and the V3 region of gp120 finally causes the membrane fusion and the genetic materials' inner flow (Berro et al. 2012).

As an ideal target of anti-HIV, the inhibitors of CCR5 block the combination between HIV-1 and the cell membrane receptor by changing the conformation of CCR5 that disturbs the recognition of gp120 or the internalization of it (Kaqiampakis et al. 2011). The virus invading to the host cells may be interrupted with the combination of CCR5 and result in the declines in HIV infection rates. Nowadays, there are several kinds of CCR5 inhibitors including CCR5 derivatives, synthetic compounds, and peptide compounds.

5.2.1.1 Derivatives of CCR5

As the natural ligands of CCR5, β-RANTES such as MIP-1α (Mikawa et al. 2005) and MIP-1β (Kim et al. 2001) (Fig. 5.2a) certainly is the antagonist of HIV-1 receptors which protects the host cells by inducing the endocytosis of CCR5 to some extent. However, it is not suitable for the β-RANTES to become real drugs on account of their short half-life period (less than 10 min) and potential inflammatory response of these natural compounds. Researches show that CC-RANTES in a high concentration can help slow disease progression, while some different studies proposed that the high concentration may also activate cells to worsen the HIV-1 infection (Trkola et al. 1999). Thus, the Chemotactic Factor RANTES becomes more aggressive than the natural ligands because the former ones hinder the internalization of the receptor while not inducing the signaling pathways.

CC-chemokine RANTES (3–68) (Schols et al. 1998) (Fig. 5.2b), missing two NH_2-terminal residues, has been isolated from leukocytes and tumor cells. It has been proved to be an effective CCR5 receptor antagonist. RANTES (9–68) (Polo et al. 2000) is another CCR5 inhibitor which missed eight amino acids of the NH_2-

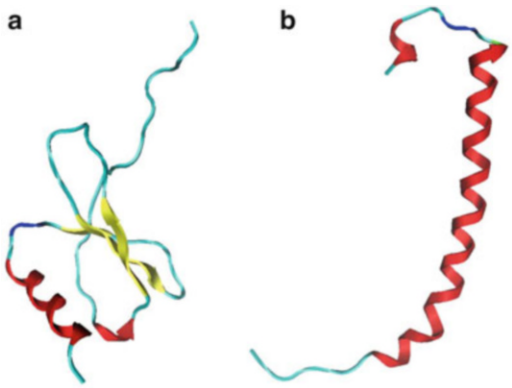

Fig. 5.2 The derivative inhibitors of CCR5. (**a**) MIP-1β. (**b**) CC-chemokine RANTES (3–68)

terminal, and the experimental data shows a lower inhibitory activity than the RANTES (3–68). Besides, other RANTES-based modified derivatives, such as AOP-RANTES, MET-RANTES, and PSC-RANTES (Lobritz et al. 2013), are also effective CCR5 antagonists. The derivatives are able to reduce the CCR5 expression level on the cell surface to realize the antiviral purpose.

5.2.1.2 Peptide Compounds

Peptide compounds specially recognize the particular extracellular region of CCR5 that has less poisonous side effect but will not be easily digested and degraded by the host (Wu et al. 2012). Appeared on the market in 2003, T20 is a peptide CCR5 inhibitor belonging to the HIV-1 fusion inhibitors which are derived from sequences 643–678 of transmembrane protein gp140. Peptide T (Maria et al. 2005) is another derivative of gp120 that is derived from the 185–192 amino acid sequences, and it has been proved to be nontoxic with inhibitory activities against HIV-1. There are also some polypeptides like peptide S, cDDR-MAP derived from CCR5 structure itself which possesses the ability of blocking the binding between gp120 and CCR5. Besides, a dodecapeptide (sequence: AFDWTFVPSLIL) screened from the peptide database by phage display has shown specific binding to CCR5 whose binding domain may belong to the ECL2 of it.

5.2.1.3 Non-peptide Compounds

Now, the non-peptide compounds are predominant in the developing of CCR5 inhibitors. This kind of antagonists, without potential inflammatory response effect, has advantages of low-cost production contrasting to the peptide compounds which also can be injected intravenously. There are several kinds of non-peptide inhibitors including TAK-779 (Ni et al. 2009), SCH-351125, maraviroc, etc. (Fig. 5.3). TAK-779, a small molecule antagonist of CCR5, has been developed by Takeda

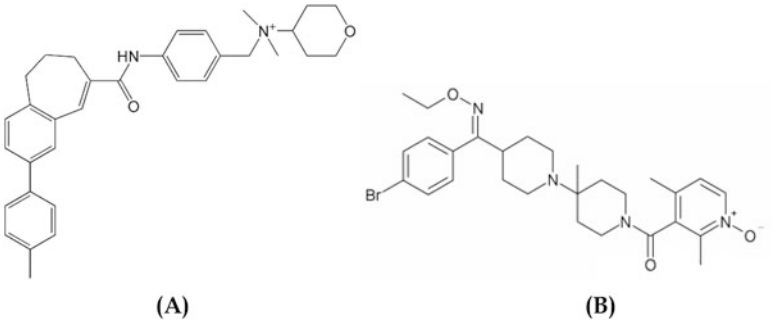

Fig. 5.3 The non-peptide inhibitors of CCR5. (**a**) Structure of TAK-779. (**b**) Structure of SCH-351125

Company in Japan and mainly used for the CCR5 receptor. As the first CCR5 drug, maraviroc has been approved for marketing in 2007, and it has been advised in the drug-combined therapy with the antiretroviral drugs. SCH-351125 (Marjan et al. 2007) is another high specific CCR5 antagonist with oxime piperidine structure which changes the conformation of extracellular domain by combining with the 1, 2, 3, and 7 transmembrane domains of CCR5. It is the first non-peptide CCR5 antagonist in the clinic that the side effect of prolonging the heart QT interval at high concentration prevents it from going further in clinical practice. But the structure reformation based on SCH-351125 has been proven to be successful. A series of derivatives have been received, in which SCH-417690 was testified to be enhanced by ten times in activity as its predecessor. Besides, without the cardiovascular side effect, SCH-417690 processed the advantage in pharmacokinetic parameters which has entered phase III clinical trial stage now.

5.2.2 The Target gp120 and Its Inhibitor

During the process of HIV-1 infecting the host cell, the viral envelope protein named gp120 primarily mixes together with the target cell membrane (Zhou et al. 2007). For this reason, the virus infection can be inhibited in the initial stage if the fusion process is blocked, which is also believed to be a promising drug therapy strategy.

HIV gp120, a member of glycoprotein, is composed of five variable regions (V1–V5) and another five relatively conservative regions (C1–C5) (Kwon et al. 2012). Researches show that there are four heparin sulfate binding sites on the surface of gp120 including V2, V3, C-terminal, and CD4 binding sites. After combining with CD4 at the last site, the other binding sites are exposed to the coreceptors like CX, CR4, or CCR5 and are easily recognizable (Schnur et al. 2011). The crystal structure of natural gp120 has been resolved in 2005, although that was from the simian immunodeficiency virus (SIV) rather than the HIV-1.

Compared with the structure binding with CD4, the natural gp120 is never found to have the bridge piece layer structure between the inner and the outer domains. The conformation of gp120 will significantly change while it combines with CD4 molecule, and a bridge piece layer structure forms between the V1/V2 and β20/β21 domains after then which commonly construct the binding site for the coreceptor in the next step (Shrivastava et al. 2012). Researches have shown that a stable α2-helix structure domain (Tan and Rader 2009) (Resides 335–352) locating on the outer region of gp120 binding with CD4 would be a target for developing new anti-HIV drugs.

5.2.2.1 Polypeptide Inhibitors

Gp120 exists in tri-polymer commonly between which the distances of any two CD4 binding pockets are 3–6 nm (Fig. 5.4). Based on this, a series of polypeptides simulating the tri-polymer CD4 have been designed in which a polypeptide G1 (ARQPSFDLQCGF) (Choi et al. 2001) simulates the Phe43 and β-folding of CD4 with good gp120 inhibiting activity. On this basis, several similar polypeptides have been synthesized after structure modification to G1, one of which even has an IC_{50} 1 μmol/L.

Another polypeptide (12p1) composed of 12 amino acids (RINNIPWSEAMM) has anti-HIV activity in vitro. It is able to combine with gp120 to prevent the binding between gp120 and CD4. Studies have demonstrated that 12pl inhibits CD4 binding with gp120 through allosteric effect rather than competitively inhibiting the binding of CD4 (Biorn et al. 2004). Recently, some researchers made a dimeric compound linked by 12pl and *Nostoc ellipsosporum* of *Cyanobacteria* (Zappe et al. 2008) which embodied stronger antiviral activity than the 12pl monomer.

5.2.2.2 Macromolecular Inhibitors

Researches indicated that solvable CD4 significantly reduced the virus load of HIV-1 in laboratory, but when it applied in clinical trials, it was weak to inhibit the viral strain. Further studies have found that some derivatives of solvable CD4 inhibit various HIV strains of which the half-time period in vivo remarkably extended. A recombinant fusion protein CD4-IgG2 designed by Progenics Pharmaceuticals Company could effectively reduce the viral load after clinical experiments (Alexandre et al. 2011). Furthermore, the induced allergic reaction and other side effects were not found that may have a good clinical application value.

The gp120 targeting broad-spectrum neutralizing antibody (Solanki et al. 2014) is another breakthrough in the research field of anti-HIV recently. These antibodies usually combine with the HIV envelope protein to prevent the virus from entering into the target cell; besides, they also clear the HIV particles and infected host cells through complement activation and other methods. Burton et al. isolated two broad-spectrum neutralizing antibodies PG9 and PG16 (Doores and Burton 2010) from

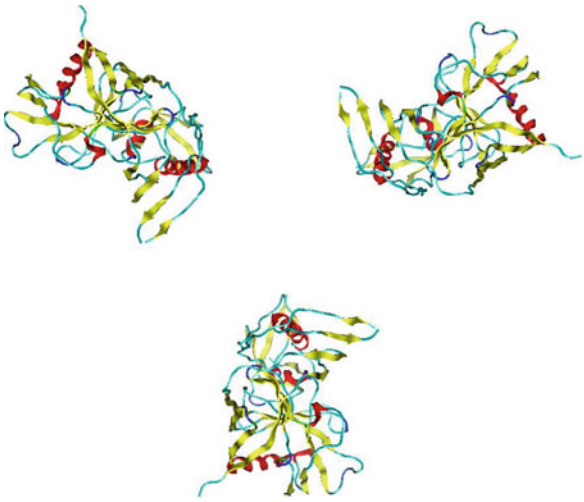

Fig. 5.4 HIV-1 gp120 forming timers on the surface of the viral membrane

the infected B-cells which neutralize two HIV subtype strains. Both of them are able to neutralize 127 and 119 plants, respectively, from the total 162 viral strains at a low concentration less than 1 mg/L which are confirmed to bind with the variable loops of conservative V1/V2 and V3 of gp120 in the next researches. Corti et al. separated another neutralizing antibody HJ16 that recognizes the binding domain of nearby CD4 (Corti et al. 2010). Experimental data showed that this antibody neutralized various subtypes of 92 HIV virus strains at a ratio of 36%. And the binding site recognized by HJ16 located in the conservative region of gp120 between the joint part of internal and external domains which may prove to be an important target for drug and vaccine design.

5.2.2.3 Small Molecular Inhibitors

The polypeptide inhibitors are the primary infusion inhibitors so far which have some shortcomings of low bioavailability and expensive cost restricting for use in clinical practice. Thus, the developing of small molecular inhibitors is necessary to increase the choices for patients. And the current developed inhibitors mainly block the binding between gp120 and CD4 or targeting to the phe43 binding pocket whose chemical structures include BMS-378806, NBD-556 [(Liu et al. 2014), (Zhao et al. 2005)], and their analogues (Fig. 5.5).

5.2.3 The Target Vif and Its Inhibitors

Innate immunity plays an important part in defending the HIV infection of human bodies, one of which called APOBEC3G (A3G) belonging to the apolipoprotein B

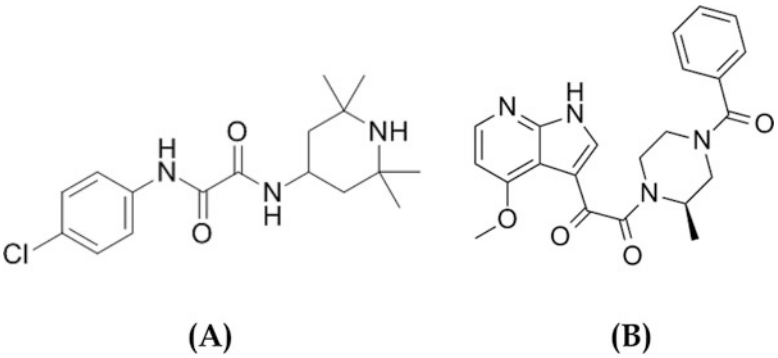

Fig. 5.5 Small molecular inhibitors of gp120. (**a**) Structure of NBD-556. (**b**) Structure of BMS-378806

mRNA-editing enzyme catalytic polypeptide protein (APOBEC) inhibits the replication of HIV-1 by cytosine deaminase mechanism (Zhou et al. 2014). Meanwhile, the virus infectivity factor (Vif) combines with A3G to induce the degradation of it that increases the risk of infection for 100 times. It is no doubt that the interaction between A3G and Vif becomes the hotspot of anti-HIV.

The structure of Vif, composed of 192 amino acid residues, contains four domains, that is, N-terminal, HCCH domain, SLQYLA, and PPLP sequence motif. The N-terminal region is a critical section of Vif in which amino acid residues 40–44 and 85–99 are the binding sites of A3G, and residues 1–21, which are highly conservative, are the tryptophan-rich domains which play an important part in recognizing and inhibiting A3G. HCCH domain contains residues H108, C114, C113, and H139 and a chelating Zn^{2+} forming a zinc finger that mediates the combining with Cullin5 (Cul5) (Wang et al. 2014). Moreover, ^{144}SLQYLA^{149} motif induces the interaction between Vif and ElonginC.

5.2.3.1 The Pharmaceutical Research Strategy Based on the Target Vif-A3G

Vif collects Cul5, ElonginC, and Rbxl to form a Skpl-cullin-F-box complex to inhibit the virus replication through A3G degradation by ubiquitin-protease way (Wang et al. 2011). There are two methods at present to reach this goal: to prevent the degradation of A3G directly or to increase the package quantity of A3G.

Based on knowledge in the region of interaction between Vif and A3G, Straska et al. screened a compound RN-18 (Nathans et al. 2008) that degraded Vif to improve the A3G level, and Shan et al. also screened IMB-26/35 (Cen et al. 2010) (Fig. 5.6) from an 8634 compound database which competitively inhibited the combining of Vif and A3G. Another approach to prevent the degradation by Vif-mediated protease way lies in the structure modification of A3G whose tiny change will significantly reduce the sensibility of Vif. Researches showed that a

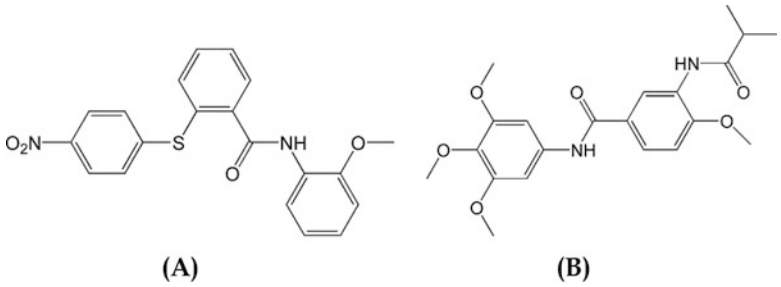

Fig. 5.6 Structure of Vif inhibitors RN-18 (**a**) and IMB-26 (**b**)

site-directed mutation D128K of A3G hindered the binding with Vif that the A3G was protected finally. Li et al. (2008) merged A3G and UBA2 together to form a fusion protein which would not be degraded by the ubiquitin. That is, the pathway of ubiquitin protease degradation has been blocked up.

Enhancing the ability of entering the progeny virus of A3G is another method to express its activity as possible. Green et al. built a Nef7-A3G fusion protein in which the Nef mutant called Nef7 increased the targeting transport efficiency of A3G while did not destroy the antiviral ability of it.

5.2.4 The Target TRIM5-α

Although HIV-1 is capable to infect numerous kinds of mammalian cells including human beings, it cannot infect some primates such as *Macaca rhesus*. The subsequent studies have found that there is a new protein in these primates' body named TRIM5-α which can effectively inhibit the replication of HIV-1 in vivo. As a critical inhibiting factor of the primate immune system to inhibit the retrovirus infection, it provides a new way for the treatment of AIDS.

5.2.4.1 Mechanism of TRIM5-αProtein Preventing the HIV-1 Infection

Researchers have found that TRIM5-α protein may package the HIV-1 capsid to hold back the genetic materials released that finally control the replication of HIV-1 in vivo (Zhang et al. 2013). After HIV-1 invading the host cells, the capsid and particle of the virus separate. Then, TRIM5-α protein seeks the released viral capsid for binding. And with the function of E3 ubiquitin-protein ligase in the RING domain (Lienlaf et al. 2011; Roa et al. 2012), it accelerates the degradation of the capsid to inhibit the replication of HIV-1 effectively. However, the existence of similar TRIM5-α protein was also confirmed in the cells of mankind whose activity of inhibiting HIV-1 was much sparser compared with the one in the monkey cells. It

may attribute to the reason of genetic variation between different species that the powers of TRIM5-α protein in diverse individuals are not the same.

5.2.4.2 The Prospect of TRIM5-αProtein for Treating AIDS

Gene therapy (Anderson 2013) opens up board prospect for HIV-1 infection by which the TRIM5-α gene can be put into the target cells and then integrate with the genetic materials of the host. With the expression products of it, the uninfected host cells will be protected. Scientists are trying to crack the gene code of TRIM5-α, after then it could be transferred into the microorganism or the in vitro cells to produce abundant TRIM5-α proteins. Based on the new protein, other ways are to develop new medicines and vaccines by genetic engineering techniques or the new animal infection models prepared by TRIM5-α proteins.

5.3 Conclusion

At present, specific drugs and targets of anti-HIV have been developed, however, human beings are still having a hard time to eradicate the risk of this virus. The reason lies in its high reproduction, high mutation, and high reorganization. Thus, we urgently need to find new targets and more effective drugs of anti-HIV for the sake of human health. Based on the recent researches, several new targets including CCR5, gp120, Vif, and TRIM5-α have been found, and some corresponding inhibitors have been gradually used in the clinic.

With more binding sites on CCR5 receptor to combine, polypeptide inhibitors may also overcome the resistance produced by the small molecular inhibitors. For this reason, the polypeptide inhibitors may be the main research directions that will cover the shortages of the later ones. On the contrary, the polypeptide inhibitors of gp120 is low in bioavailability with expensive price, so the development of some small molecular entry inhibitors will be necessary. As the crystal structures of gp120 antigen/antibody complex have been resolved, the virtual screening may be effective technological means for searching new small molecular inhibitors of gp120. While the inhibition mechanisms have been elucidated, both Vif and TRIM5-α are hot new anti-HIV targets in recent years toward which some potential active compounds have been designed or screened. It is believed that the main tasks of anti-HIV in the future would be to find effective special targets so as to develop more powerful, high sensitive, and low side effect inhibitors.

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