

John C. Tilton and Robert W. Doms

Introduction to entry inhibitors in the management of HIV infection

Summary

The HIV envelope proteins gp120 and gp41 act sequentially to mediate viral attachment, CD4 binding, coreceptor binding, and fusion of the viral and host membranes. The emerging class of antiretroviral agents collectively known as entry inhibitors interfere with this multi-step process of viral attachment and entry into target cells. Entry inhibitors have diverse mechanisms of action, but all target the HIV envelope proteins directly, or, in the case of coreceptor inhibitors, indirectly. Due to the diversity of the HIV envelope proteins, it is apparent that primary HIV isolates from patients treated with these agents vary significantly in their baseline susceptibility to these inhibitors, and that complex pathways of viral resistance will eventually emerge. Viral resistance to entry inhibitors will undoubtedly alter the way that HIV envelope interacts with its receptors and therefore may alter the tropism—and thereby the pathogenesis—of HIV infection. These factors will necessitate close clinical monitoring of resistance mutations in patients treated with these agents. Currently, the fusion inhibitor enfuvirtide (T-20, Fuzeon) is the only entry inhibitor approved for the treatment of HIV-infected patients, but CD4 and coreceptor inhibitors are in various stages of testing. The diverse mechanisms of action of these agents raise the possibility that these drugs may be synergistic in combination with other entry inhibitors or other classes of antiretroviral agents. Finally, continued research into the process of HIV entry into target cells will be necessary to further define the interactions between the envelope proteins and their cellular receptors that will allow for refinement of entry inhibitor design. Together, these factors make the entry inhibitors a particularly interesting class of antiretroviral agent that have the potential to significantly improve treatment of HIV-infected patients and to advance the understanding of HIV entry, tropism, and pathogenesis.

Key words: HIV, Env, gp120, gp41, CD4, coreceptor, fusion, CD4-binding site, coreceptor-binding site, entry inhibitor, enfuvirtide, BMS-806

Laurence Vergne and Martine Peeters

The challenge of HIV sequence diversity in the envelope glycoproteins

Summary

One of the major characteristics of the human immunodeficiency viruses (HIVs) is their extremely high genetic variability, which makes HIV one of the fastest evolving among many other human pathogens. This diversity is the result of a combination of several factors such as the high error rate and recombinogenic nature of the reverse transcriptase together with the fast turnover of virions in HIV-infected individuals. This diversity is observed worldwide, with a heterogeneous geographical distribution of HIV-1 subtypes and CRFs, but also a high inpatient diversity (often exceeding 5% in *env*) is seen. The most variable part of the HIV genome is the envelope (*env*) gene, and the overall rate of inpatient divergence of the *env* gene is close to 1% per year. The variability of the *env* gene, among the different HIV-1 groups, subtypes worldwide and quasispecies observed within the patient, together with the different regions in the envelope glycoproteins involved according to which step in viral entry is the targeted by the molecule, make it a real challenge to design antiretroviral drugs in this region.

Key words: HIV, genetic diversity, Env glycoproteins (Gp120 and Gp41), subtypes, recombinant forms, geographical repartition, quasispecies, natural polymorphisms

Stefan Pöhlmann and Michel J. Tremblay

Attachment of human immunodeficiency virus to cells and its inhibition

Summary

In recent years the cellular entry of human immunodeficiency virus type-1 (HIV-1) emerged as an interesting target for preventive and therapeutic agents. The viral envelope protein (Env) facilitates delivery of the viral nucleocapsid into the cellular lumen by fusing the viral membrane with the cytoplasmic membrane of the host cell. The membrane fusion activity of Env is activated by engagement of the cellular receptors, CD4 and a chemokine coreceptor, usually CCR5 or CXCR4. While the interactions of Env with CD4 and coreceptor are indispensable for viral entry and offer multiple targets for intervention, the mere attachment of virus to cells can proceed in the absence of these receptors. Attachment can be promoted by the interaction of surface molecules on cells with their cognate ligands incorporated into the viral membrane during release of HIV-1 from infected cells. Alternatively, cellular lectins can capture virions by binding to glycans on Env. Both processes can profoundly increase viral infectivity and might contribute to HIV-1 spread in and between individuals. Here, we will review the molecular interactions underlying HIV-1 attachment mediated by host cell factors incorporated into the viral envelope or by cellular lectins and will discuss strategies to prevent these processes.

Key words: HIV, attachment, gp120, host cell, ICAM-1, DC-SIGN, DC-SIGNR

Pin-fang Lin, John Kadow and Louis Alexander

Inhibitors that target gp120-CD4 interactions

Summary

Gp120 binding with CD4 is the essential first step of the HIV-1 entry process and, therefore, the conserved CD4 binding site in gp120 provides an attractive antiviral target. This chapter discusses recent encouraging progress made in the development of this class of antiviral agents. The profiles, current development status, issues, and potential of these inhibitors are summarized. These agents include: (1) small molecule inhibitors directly targeting gp120 (BMS-378806 and its analogs, BMS-488043, NBD-556, NBD-557, and CD4 mimetic compounds), (2) biologic, peptide, or large molecule inhibitors of gp120 (a CD4-IgG fusion protein PRO-542, a chimeric protein sCD4-17b, CD4 mimetic peptides, and a neutralizing monoclonal antibody IgG1b12), and (3) inhibitors targeting CD4 or CD4 expression (CADA, which decreases cell surface and intracellular CD4, NSC-13778, which competes with gp120 for CD4 binding, and TNX-355, a humanized monoclonal antibody against CD4). Importantly, the orally available BMS-488043, PRO542 protein and TNX-355 monoclonal antibody have demonstrated clinical efficacy, which validates interruption of the gp120/CD4 interaction as a viable antiviral approach. This new class of agents is expected to be effective against viruses resistant to marketed drugs (targeting HIV-1 reverse transcriptase, protease or fusion), and thus offers excellent potential for new treatment options.

Key words: HIV-1 entry, envelope, CD4, gp120 inhibitors, BMS-378806, BMS-488043, NBD556, PRO-542, sCD4-17b, CD4M33, IgG1 b12, CD4 inhibitors, CADA, NSC13778, TNX-355

Julie M. Strizki and Donald E. Mosier

Inhibitors that target gp120 interactions with coreceptor

Summary

The discovery that HIV-1 entry into target cells requires binding of both CD4 and one of two chemokine receptors, CCR5 or CXCR4, provided two new targets for viral inhibition. The fact that individuals with a homozygous coding region deletion in the CCR5 gene were naturally resistant to HIV-1 infection yet suffered no apparent clinical defects (although this view is being modified) provided an unusual genetic validation of CCR5 as a therapeutic target. Three classes of inhibitors targeting HIV coreceptors have been developed: small molecules, large peptides mimicking the natural chemokine ligands, and antibodies. Several of the small molecule inhibitors are in late stage clinical trials. This review will briefly describe the evolution of the HIV-1 envelope that dictates coreceptor use, and summarize recent progress and some setbacks in the development of coreceptor inhibitors.

Key words: human immunodeficiency virus type 1 (HIV-1), C-C chemokine receptor 5 (CCR5), C-X-C chemokine receptor 4 (CXCR4), RANTES (CCL5, regulated upon activation, normal T cell expressed and secreted), R5X4, (R5)X4

Wei Wang and Carol D. Weiss

Inhibitors that target fusion

Summary

Fusion inhibitors target the envelope glycoprotein (Env) after Env binds host cell receptors but before it catalyzes fusion with the host cell membranes. Inhibiting this early step in the viral life cycle offers unique advantages and disadvantages for developing novel drugs. Blocking HIV before it gains entry into cells is highly desirable, but intercepting Env during the short window when it is undergoing conformational changes at the host cell surface poses challenges for drug access. Nonetheless, peptides targeting this fusion step have proven to be potent inhibitors of HIV infection. The recent advancement of one of these peptide fusion inhibitors (Enfuvirtide/T-20) into the clinic raises hope that other agents in this new class of antiretrovirals will follow soon. This chapter reviews mechanistic aspects of how fusion inhibitors block HIV entry, potential approaches for the development of new inhibitors, and how Env variation, resistance mutations, and host cell factors can influence sensitivity to fusion inhibitors.

Key words: HIV entry, HIV fusion, peptide inhibitor, fusion inhibitor, entry inhibitor, T-20, N peptides, C peptides, six-helix bundle, gp41, membrane fusion

Clyde Hart and Tammy Evans-Strickfaden

HIV-1 entry inhibitors as microbicides

Summary

Sexual transmission of HIV-1 is the major route for infection of both men and women. Although consistent use of male condoms has been shown to greatly reduce HIV-1 sexual transmission, there are significant gender inequality, societal, and interpersonal intimacy issues that have limited their use in many high-risk populations throughout the world. To provide an alternative to condom use, topically applied vaginal microbicide compounds that have anti-infective activity against HIV-1 and possibly other sexually transmitted infections

are being developed and clinically tested. HIV-1 entry/fusion inhibitors constitute the largest category of candidate vaginal microbicides that are currently being tested *in vitro* and in clinical trials. These include human monoclonal antibodies, chemokine analogs, HIV-1 envelope protein ligands, carbohydrate binding proteins, and polyanions. *In vitro* evaluations and animal studies have determined product efficacy against the CCR5 co-receptor using viruses that are most associated with sexual transmission. To increase the potency of vaginal microbicides, more recent products include those that combine entry inhibitors with other classes of HIV-1 anti-infectives.

Key words: vaginal microbicide, HIV-1, sexual transmission, entry inhibitor, cervical-vaginal mucosa, polyanion, human monoclonal antibody, chemokine analog, gp120/gp41 ligand, carbohydrate binding protein

Lynn Morris, Mia Coetzer, Elin S. Gray, Tonie Cilliers, Kabamba B. Alexandre, Penny L. Moore and James M. Binley

Entry inhibition of HIV-1 subtype C isolates

Summary

Almost all entry inhibitors have been developed and tested using HIV-1 subtype B viruses. While those that target the cellular receptors, CD4 and chemokine coreceptors, are likely to be effective against all genetic subtypes of HIV, entry inhibitors that target the virus may be compromised by the genetic diversity of the envelope glycoprotein. In this review we focus on HIV-1 subtype C, which is the most globally prevalent virus and for which some data is available. Evidence suggests that for most entry inhibitors, efficacy against subtype C viruses is comparable with subtype B, although certain anti-envelope monoclonal antibodies reveal that differences between these two subtypes do exist. Since entry inhibitors, particularly if they are to be used in microbicide formulations or other prevention strategies, are likely to be most useful in countries where subtype C dominates, it is imperative that they are tested for efficacy, or more pertinently, designed with this subtype in mind.

Key words: HIV-1 subtype C, envelope, genetic variation, CCR5, CXCR4, V3, entry inhibitors, prediction algorithms, transmitted variants, monoclonal antibodies, antibody neutralization, microbicides

Eoin Coakley

The utility of coreceptor typing in the clinic

Summary

HIV utilizes the CD4 receptor and a coreceptor either CXCR4 or CCR5 to enter host cells. Some viruses utilize CCR5 only (R5), some use CXCR4 only (X4) and some are able to utilize either coreceptor (R5X4 or dual tropic). Circulating HIV may also exist as mixtures of viruses with distinct tropism profiles (mixed tropism). Current testing methods do not readily distinguish between dual tropic virus and populations of mixed tropism. For this reason the term dual/mixed (DM) tropism is used.

Coreceptor utilization is not fixed at primary infection but may evolve over time. Early in HIV infection viruses are typically R5 tropic. In contrast, in highly treatment experienced individuals, or those with late stage disease, X4 and dual viruses are observed with increased frequency. The emergence of such CXCR4 utilizing HIV over time in a given individual has been associated with accelerated HIV disease progression and earlier onset of AIDS.

Intriguingly, individuals who are homozygous for the *ccr5*Δ32 mutation lack fully functional CCR5 on the cell surface. Such individuals appear to be otherwise healthy and are resistant to infection by R5 HIV. New pharmacologic agents blocking CCR5 coreceptor utilization are currently in clinical trials. Such agents would be an important addition to the current anti-HIV armamentarium. However, because of the potential for differences in tropism from person to person, and over time, it is likely that a tropism screening assay would be required for optimal utilization of this new drug class. This chapter aims to summarize early and more recent clinical data relevant to potential coreceptor typing in the clinic.

Key words: tropism, coreceptor, antagonist, screening

Sonya L. Heath and J. Michael Kilby
Future clinical prospects for entry inhibitors
Summary

In this chapter, we compare and contrast the diverse entry inhibitors under development, or recently approved, in regard to clinically relevant characteristics (potency, pharmacokinetics, toxicity, resistance), with the clinical experience of currently available RT- and PI-based regimens. We describe some of the key lessons learned from the early clinical development of several HIV entry inhibitors, and discuss what these findings may mean in terms of future prospects, both promises and pitfalls, for this novel therapeutic class.

Michael L. Greenberg
Enfuvirtide: from basic science to FDA approval
Summary

Enfuvirtide is the first in a new class of drugs that block HIV entry to gain approval for use in treatment of HIV-1 infection in treatment-experienced patients with ongoing HIV-1 replication despite antiretroviral therapy. The mechanism of action of enfuvirtide targets the process of virus-cell fusion which is brought about by the HIV-1 gp41 transmembrane glycoprotein. Enfuvirtide was developed to address an unmet medical need for treatment-experienced patients with limited options available to suppress their virus. As new agents have become available to combine with enfuvirtide, the percentage of such patients that can become fully suppressed is approaching what can be achieved in first line regimens. This chapter reviews the early investigations that led to the discovery of enfuvirtide and establishment of its mechanism of action. In addition, the chapter reviews the early preclinical studies and clinical studies that resulted in the approval of enfuvirtide, the first fusion inhibitor. Determinants of susceptibility and mechanisms of resistance are discussed as are the potential impacts on viral fitness and virus pathogenicity.

Key words: enfuvirtide, fusion inhibitor, entry inhibitor, antiviral agents, resistance, mechanism of action, mechanism of resistance, fitness, pathogenicity, virologic response, immunologic response, immune activation, apoptosis

Roy M. Gulick

Targets for drug development – past and present

Summary

Currently, there are 22 antiretroviral drugs approved for the treatment of HIV infection. These drugs provide antiretroviral activity by targeting and interfering with distinct steps of the life cycle of HIV. The efforts of basic and clinical scientists in academia, government, and industry synergized to speed the discovery and development of effective antiretroviral therapy. In 1987, the first HIV drug, zidovudine (AZT), a nucleoside analogue that targets the HIV reverse transcriptase enzyme, was approved. In 1995-1996, two additional classes, non-nucleoside inhibitors of the reverse transcriptase enzyme, and inhibitors of the HIV protease enzyme were approved. The first step in the life cycle of HIV, viral entry, consists of 3 substeps: CD4 receptor attachment, chemokine receptor attachment and membrane fusion. In 2003, the first HIV entry inhibitor, enfuvirtide (a fusion inhibitor) was approved for the treatment of HIV infection. Currently, investigational HIV entry inhibitors targeting CD4 receptor attachment, chemokine receptor attachment (both the CCR5 and the CXCR4 receptors), and membrane fusion are in clinical development.

Key words: nucleoside analogue reverse transcriptase inhibitor (NRTI), non-nucleoside analogue reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), entry inhibitor (EI), fusion inhibitor, CD4 attachment inhibitor, CCR5 inhibitor, CXCR4 inhibitor, enfuvirtide, maraviroc, vicriviroc, TNX-355, AMD 070, PRO 542



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