Hans Jäger (Ed.)

Entry Inhibitoren

Neue Formen der HIV-Therapie

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Mit 44 Abbildungen und 5 Tabellen

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Dr. med. Hans Jäger
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Vorwort

Der rasche Fortschritt in der HIV-Forschung wird durch die erfolgreiche Entwicklung der Substanzklasse »Entry-Inhibitoren« erneut eindrucksvoll belegt. Bei keiner vergleichbaren Erkrankung sind direkt für den Patienten – auch deutlich spürbare – Optimierungen des Managements und Verbesserungen der Prognose in ähnlich hohem Ausmaß sichtbar.

Nach zögerlichen Anfangserfolgen von meist vorübergehender Dauer ist seit Mitte der 90er Jahre eine nachhaltige Verbesserung der Prognose eingetreten. Der Horizont ist offen. Patienten können in den meisten Situationen Lebensentscheidungen so treffen, wie sie es auch ohne HIV-Infektion tun würden.

Hierfür waren drei Faktoren ausschlaggebend. Seit Mitte der 90er Jahre liegt ein besseres Verständnis der HIV-Pathogenese vor, die Menge der Viren im Blut wurde messbar und es konnten erfolgreich Dreifachkombinationstherapien eingesetzt werden

Ebenfalls Mitte der 90er Jahre wurden die spezifischen Chemokinrezeptoren CXCR4 und CCR5 identifiziert. Beide sind wichtige Korezeptoren beim Eintritt von HIV in die Zielzelle. CCR5 ermöglicht als Korezeptor die Infektion durch CCR5(R5)-trope Viren vor allem von aktivierten CD4-Zellen und Makrophagen, wobei das HIV-Hüllglykoprotein (ENV) zunächst mit den CD4-Rezeptoren, dann mit dem Korezeptor interagiert. CXCR4(R4)-trope Viren können darüber hinaus auch ruhende CD4-Zellen infizieren. Sie stellen das pathophysiologische Korrelat der Ende der 80er Jahre beschriebenen SI-(Synzytium induzierende) Virusvarianten dar.

CCR5(R5)-Inhibitoren – mit Maraviroc (Celsentri) wurde 2007 in den USA und Europa die erste Substanz dieser Klasse zugelassen – stellen eine wichtige Erweiterung des therapeutischen Arsenals für HIV/AIDS-Patienten dar, bei denen R5-trope Viren nachweisbar sind.

R5-Virusstämme werden nach derzeitigem Kenntnisstand effizienter übertragen als X4-Virusstämme. Sie finden sich vor allem in den frühen Stadien der HIV-Infektion. Therapienaive Patienten weisen zu ca. 80%, vorbehandelte Patienten zu ca. 55% R5-trope Viren auf. Die überwiegende Anzahl der übrigen Viren ist R5/X 4 »dual mixed«. Ein reiner X4-Tropismus ist selten.

Die Ergebnisse großer klinischer Studien (MOTIVATE 1 und 2), die 2007 veröffentlicht wurden, zeigen einen hohen therapeutischen Nutzen bei Patienten mit fortgeschrittener HIV-Infektion und R5-tropen Viren. Bei diesen Patienten war der Effekt mit dem der Integraseinhibitoren vergleichbar.

Auch bei therapienaiven Patienten (Merit-1- und -2-Studien) wird ein Behandlungspotential erkennbar, wenngleich die Non-Inferiorität gegenüber der Vergleichssubstanz Efavirenz bezüglich des Anteils der Patienten mit Viruslast < 50 Kopien/ml zu Woche 48 nicht nachweisbar war (64% für Maraviroc, 69% für Efavirenz).

Allerdings zeigten die mit Maraviroc behandelten therapienaiven Patienten einen höheren CD4-Zell-Anstieg, weniger Nebenwirkungen und eine geringere Zahl von malignen Erkrankungen. Erste Studien untersuchen den Einsatz von Maraviroc in Kombination mit anderen Substanzen zur möglichen HIV-Eradikation.

Dieser Band soll die derzeitigen klinischen Möglichkeiten und Managementerfahrungen beim Einsatz der neu zugelassenen Substanz Maraviroc (Celsentri) beschreiben und die pathophysiologischen Grundlagen erläutern. Er soll zudem die Herausforderungen, insbesondere im Rahmen der Tropismusbestimmung, aufzeigen und praktische Hinweise, etwa zu den Dosierungsadaptationen, vermitteln.

München, im April 2008
Hans Jäger

Inhaltsverzeichnis

VI Sonderthema

Autorenverzeichnis

Bara, Yves A.
Pfizer Pharma GmbH
Postfach 4949
76032 Karlsruhe
Yves-andre.bara@pfizer.com

Beer, Klaus
Pfizer Pharma GmbH
Postfach 4949
76032 Karlsruhe
klaus.beer@Pfizer.com

Behrens, Georg
Medizinische Hochschule Hannover
Abteilung Klinische Immunologie
Carl-Neuberg-Str. 1
30625 Hannover
behrens.georg@mh-hannover.de

Esser, Stefan
Universitätsklinikum Essen
Hautklinik
Hufelandstr. 55
45122 Essen
stefan.esser@uni-essen.de

Fätkenheuer, Gerd
Klinikum I für Innere Medizin der
Universität Köln
Arbeitsgruppe Infektiologie
Joseph-Stelzmann-Str. 9
50924 Köln
g.faetkenheuer@uni-koeln.de

Gölz, Jörg
HIV-Schwerpunktpraxis Berlin
Kaiserdamm 24
14057 Berlin
goelz@snafu.de

Harrer, Thomas
Universitätsklinikum Erlangen
Medizinische Klinik III
Krankenhausstr. 12
91054 Erlangen
thomas.harrer@med3.imed.uni-erlangen.de

Heiken, Hans
Georgenstr. 46
30159 Hannover
dr.heiken@email.de

Hoffmann, Christian
Infektionsmedizinisches Centrum Hamburg
Grindelallee 35
20146 Hamburg
grindel@ich-hamburg.de

Jäger, Hans
MVZ Karlsplatz
Stachus 8
80335 München
info@jajaprax.de

Kaiser, Rolf
Universität Köln
Institut für Virologie
Fürst-Pückler-Str. 56
50935 Köln
rolf.kaiser@uk-koeln.de

Kirchhoff, Frank
Universität Ulm
Albert-Einstein-Allee 11
89081 Ulm
Deutschland
frank.kirchhoff@uniklinik-ulm.de

Klimkait, Thomas
InPheno AG
Vesalgasse 1
CH-4051 Basel
thomas.klimkait@inpheno.com

Lengauer, Thomas
Max-Planck Institut für Informatik
Computational Biology and Applied
Algorithmics
Campus E1 4
66123 Saarbrücken
lengauer@mpi-sb.mpg.de

van Lunzen, Jan
Universitätsklinik Hamburg-Eppendorf
Medizinische Klinik u. Poliklinik
Martinistr. 52
20246 Hamburg
v.lunzen@uke.uni-hamburg.de

Martinez-Cajas, Jorge
McGill University AIDS Center,
Jewish General Hospital
3755 Cote-Ste-Catherine Road
Montreal, Quebec H3T 1E2
Canada
jorge.martinez2@mail.mcgill.ca

Münch, Jan
Universitätsklinikum Ulm
Institut für Virologie
Albert-Einstein-Allee 11
89081 Ulm
jan.muench@uniklinik-ulm.de

Nattermann, Jacob
Universitätsklinikum Bonn
Medizinische Klinik und Poliklinik I
Sigmund-Freud-Str. 25
53105 Bonn
jacob.nattermann@ukb.uni-bonn.de

Nelson, Mark
Chelsea and Westminster Hospital
369 Fulham Road
London SW109NH
UK
mark.nelson@chelwest.nhs.uk

Panos, George
10, Skoufa Str.
Kolonaki
106 73 Athens
Greece
panmedix@otenet.gr

Perros, Manos
Pfizer Global Research and Development
Sandwich
Kent CT13 9NJ
United Kingdom
Manos.perros@pfizer.com

Saleta, Sierra
Universität Köln
Institut für Virologie
Fürst-Pückler Str. 56
50935 Köln
Saleta.Sierra-Aragon@uk-koeln.de

Sander, Oliver
Max-Planck Institut für Informatik
Computational Biology and Applied
Algorithmics
Campus E1 4
66123 Saarbrücken
osander@mpi-sb.mpg.de

Stellbrink, Hans-Jürgen
Infektionsmedizinisches Centrum Hamburg
Grindelallee 35
20146 Hamburg
grindel@ich-hamburg.de

Thielen, Alexander
Max-Planck Institut für Informatik
Computational Biology and Applied
Algorithmics
Campus E1 4
66123 Saarbrücken
athielen@mpi-inf.mpg.de

Wainberg, Mark
McGill University AIDS Centre
Jewish General Hospital
3755, Cote Ste-Catherine Road
Room 318
Montreal, Quebec H3T 1E2
mark.wainberg@mcgill.ca

Walter, Hauke
Universitätsklinikum Erlangen-Nürnberg
Nationales Referenzzentrum für Retroviren
Schlossgarten 4
91054 Erlangen
hauke.walter@viro.med.uni-erlangen.de

Westby, Mike
Pfizer Global Research and Development
Sandwich
Kent CT13 9NJ
United Kingdom
mike.westby@pfizer.com

Teil I Basics

Viral (HIV) Entry: How Does It Work?

George Panos and Mark Nelson

HIV Life (Replication) Cycle

HIV life (replication) cycle involves attachment and fusion of the HIV particle with host target cells to initiate the infectious cycle. Entry into the host cell results in conversion of the viral genes from an RNA form to a DNA form and integration of the viral genetic material into the chromosomes of the now infected cell, where it persists for the life of the host cell, resulting in replication and budding forming new virions that are released from the infected host cells.

Pathophysiology of Human Host Cell Infection by HIV

HIV can infect macrophages, CD4 T cells and a subgroup of dendritic cells (DC) (Pope 1993; Spira et al. 1996; Zhang et al. 1998, 1999). HIV can infect CD4- and CCR5-expressing dendritic cells (DC), macrophages and T cells in the underlying mucosal tissues. Dendritic cells, abundant in vaginal and other mucosal surfaces, express CD4, CCR5, DC-SIGN and other C-type lectin receptors that facilitate the capture and infection by HIV and SIV (Frank and Pope 2002; Lee et al. 2001). DCs capture HIV particles through C-type lectin receptors and transport them to lymphoid tissue to induce an immune response by provoking activation of CD4 cells (Pope 1993); DCs can be infected by HIV through a CCR5-dependent mechanism (*cis infection*), or can merely act as transporters HIV without becoming infected by binding DC-SIGN to carbohydrates on gp120 (*trans-transmission model*). The *cis* and trans pathways of transferring HIV are not mutually exclusive (Kawamura et al. 2005). Infection in CD4 T cells is enabled by DC-T-cell conjugates, which spread infection to more CD4 T lymphocytes (Pope et al. 1994, 1995). When viruses reach the lymphoid tissue they provoke activation of CD4 T cells which acquire a memory phenotype (CD4+RO+CCR+) (Jenkins et al. 2001). The activated memory subset, which expresses higher CCR5 than CXCR4 levels, is the main producer of virus in vivo (Zhang et al. 1999; Gupta et al. 2002; Douek 2003). Also, gut associated lymphoid tissue is rich in activated memory CD4 T cells, which has been found to be the main site of early replication in both macaques and humans (Veaze et al. 1998; Brenchley et al. 2004; Mehandru et al. 2004).

CCR5 (R5) viruses predominate in the early stages of infection irrespective of the route of transmission vis a vis sexual, parenteral or vertical (Moore et al. 2004; Lederman et al. 2004). CCR5 variant viruses are responsible for the establishment of infection since they appear to

be more efficiently transmitted initially than CXCR4 viruses (Pope and Haase 2003). CXCR4 (X4) variants tend to emerge in later HIV disease stages and are associated with a more rapid CD4 cell depletion and progression to AIDS (Schuitemaker et al. 1992). Progression of HIV-1 infection from asymptomatic stages to AIDS correlates with a switch in viral co-receptor use from R5 to X4 tropic isolates in about half of the patients studied (Connor et al. 1997).

Essential HIV Particle and Host (Target) Cell Components to Effect HIV Entry

Essential prerequisite that HIV-1 particles infect human target cells such as macrophages, CD4 T cells and a subgroup of DCs is that the host (target) cell surface possesses receptors that HIV can attach and utilise to gain entry. Two viral surface membrane proteins have to interact with two host cell membrane proteins in a complex and sequential manner.

Viral Proteins

The viral proteins necessary for HIV-1 entry are surface protein gp120 and the transmembrane protein gp41; both encoded by the envelope gene (env) which is translated as a single polyprotein gp160 and subsequently processed by proteolytic cleavage. Both gp41 and gp120 proteins (gp120-gp41) associate with each other forming hetero-trimeric structures (from the Greek meaning two unified entities composed of three parts each), a trimer of three gp120 and three gp41 molecules, which are integrated within the viral membrane on virus assembly forming the envelope glycoprotein spikes (Chan and Kim 1998; Wyatt and Sodroski 1998; Popovic et al. 1983). The envelope glycoprotein spikes, on the surface of virus particles, comprise an outer surface gp120 non-covalently linked to a transmembrane gp41. The gp160 spike (gp120-gp41) contains binding domains, for both the primary CD4 receptors and chemokine CCR5, CXCR4 co-receptors (Barre-Sinoussi et al. 1983; Dragic et al. 1996). The interaction between the primary CD4 receptor and gp120 is conserved among all primate lentiviruses.

Host (Human) Target Cell Proteins

The host (target) cellular proteins required for HIV-1 trimeric envelope gp120-gp41 attachment and entry by fusion, are a triad of primary receptors, the CD4 receptors and a triad of adjacently situated co-receptors, the CCR5 or the CXCR4, two kinds of co-receptors that are used by all HIV strains (Klatzmann et al. 1984; Alkhatib et al. 1996; Dragic et al. 1996; Edwards et al. 2001).

Although more than a dozen types of co-receptors have been described, only the two co-receptor variants known as CCR5 and CXCR4 are used by all HIV-1 strains (Alkhatib et al. 1996; Dragic et al. 1996; Liu et al. 1996; Samson et al. 1996; Murphy et al. 2000). These co-receptors belong to the chemokine family of transmembrane spanning receptors coupled to a G-protein signalling pathway: the CC chemokine receptor 5 (CCR5) which binds the chemotactic chemokines, the monocyte inflammatory protein (MIP-1a, and MIP-1b), RANTES (regulated upon activation normal T-cell express and secreted), and the CXC chemokine receptor

4 (CXCR4) which binds the stromal derived factor SDF-1 as ligand (Huang et al. 1996). These soluble factors produced as chemokines in the tissue milieu or produced endogenously by target cells can have a major influence on tropism. The CCR5 receptor is used by macrophage (M-tropic) viruses and CXCR4 is used by T-lymphocyte (T-tropic) virus.

Concept of Co-Receptors in HIV Entry

The concept that co-receptors play a crucial role in HIV disease became evident when a common mutational variant of the CCR5 coding gene known as the Δ32 was discovered in 1996 (Dean et al. 1996; Benkirane et al. 1997; Wu et al. 1997; de Roda et al. 1999, Marmor et al. 2001). This CCR5 genetic variant results in the production of non-functional CCR5 co-receptors. Persons with two normal copies of the CCR5 gene predominate in the population and are susceptible to HIV infection.

Persons who inherit two copies of the CCR5 Δ32 variant from their parents known as Δ32 homozygotes have no functional CCR5 co-receptors and appear to be highly resistant to HIV infection (Dean et al. 1996; Benkirane et al. 1997; Wu et al. 1997; de Roda et al. 1999; Marmor et al. 2001).

Δ32 heterozygotes inherit one copy of the CCR5 Δ32 variant from one parent and a normal form from the CCR5 gene from the other parent. Δ-32 heterozygotes can become infected with HIV but disease progression is significantly delayed compared to those who have two normal copies of the CCR5 gene. Heterozygotes express a decreased number of CCR5 receptors and have a slower rate of disease progression (Dragic et al. 1996; Feng et al. 1996; Berger et al. 1998). An HIV particle that is unable to enter the host target cell cannot infect it, and it cannot replicate.

Therefore, attention to this co-receptor as an antiretroviral target came from genetic evidence of a naturally resistant to HIV-1 infection human population, with a homozygous 32 base pair deletion (Δ32-ccr5) in the CCR5 coding region failing to express CCR5 on the host cell surface and with little or no apparent impact on their immune status or general health.

HIV-1 Chemokine Co-Receptor Tropism

Different HIV strains differ in their ability to use the major co-receptors to achieve entry into the host cell. In addition to binding to the primary CD4 receptor a second adjacent co-receptor is required for HIV to interact with so as to gain entry into host target cells. CCR5 and CXCR4 are the major chemokine co-receptors used by HIV to enter into human host cells. Some HIV strains only use the CCR5 coreceptor, some only the CXR4 coreceptor while other viruses known as dual tropic use both or either. An HIV infected individual may have only the CCR5 using virus, only the CXR4 using virus or a mixture of CCR5, CXCR4 or dual tropic using viruses (Deng et al. 1996). Based on co-receptor use, HIV-1 strains were classified according to their tropism: CCR5-tropic (R5), CXCR4-tropic (X4), or dual-tropic (R5/X4) (Deng et al. 1996; Liu et al. 1996; Samson et al. 1996; Murphy et al. 2000); this corresponded to previous observations where non-syncytium inducing (NSI) viral phenotype was consistent with replicating in monocyte-macrophages (M-tropic) linked to less virulent strains, whereas syncytium-inducing (SI) viral phenotype was consistent with replicating in T lymphocytes (T-tropic) and linked with more virulent strains, suggesting that tropism may be related with

virulence and disease progression or stage of disease (Tersmette et al. 1988; Bozzette et al. 1993, Koot et al. 1993, Spijderman et al. 1998).

Chemokine co-receptor tropism of HIV is associated with CD4 cell counts, HIV-1 RNA levels, and NK cell counts. The presence of mixed/dual-tropic CCR5/CXCR4 populations or CXCR4 using virus may be seen at all CD4 cell counts and viral loads but is more common at lower CD4 cell counts and higher viral loads. Hence, in the early phase of infection the CCR5 using virus predominates in most patients whereas in the late phase of infection, HIV strains capable of using CXR4 co-receptors often emerge (Moyle et al. 2005).

HIV Entry

Overview

The first step in HIV life cycle is viral attachment to the primary CD4 receptor on the host (target) cell surface. The next step for viral entry involves a cascade of molecular interaction events between HIV viral envelope glycoprotein gp120 and two host (target) cell surface receptors, the primary CD4 receptor and a co-receptor, the CCR5 or the CXCR4, two co-receptors that are used by all HIV strains. The viral particle envelope gp120 and host cell primary CD4 receptor and CCR5 or CXCR4 co-receptor come to closer proximity, inducing a conformational change in gp120 that allows it to bind to the co-receptor, resulting in a viral two point binding with the target cell. Co-receptor binding triggers conformational changes in the gp41 subunit, leading to insertion of its N terminal fusion peptide into the host cell's membrane. Fusion ensues (joining of the viral and CD4 T cell membranes), which results in release of the viral genome into the host (target) cell cytoplasm.

Thus, three main steps for virus entry into the host (target) cell are required, namely

1. attachment of the virus,
2. interaction of the virus with the co-receptors, and
3. fusion of the virus.

Attachment of the Virus

The first step in HIV entry by fusion (Harrison 2005) involves the high affinity attachment of the CD4 binding trimeric domains of the viral envelope gp120 to the corresponding primary CD4 receptors on the host (target) cell surface (Sattentau et al. 1988; Weiss et al. 1988). This means that three viral envelope gp120 (trimeric) molecules, comprising the outer part of one envelope glycoprotein spike on the surface of the viral particle, bind with three molecules of primary CD4 receptors situated correspondingly on the host cell surface, thus stabilizing the virus proximally to the host cell surface.

Interaction of the Virus with the Co-Receptors

Once the three viral envelope gp120 molecules are bound with the three primary CD4 receptors, the viral envelope trimeric complex undergoes a structural change, exposing the chemokine-binding domains of gp120 known as variable loops – V1/V2 and V3 variable loops

(»flaps«) (Kwong et al. 1998; Myszka et al. 2000; Cormier et al. 2002) which are separated by a »bridging sheet« – thus allowing them to interact (»grip«) with the exposed adjacently positioned target chemokine co-receptor (i.e. CCR5, or CXCR4).

Flexible regions in the primary CD4 receptor between domains 2 and 3 as well as between domain 4 and the membrane allow further proximal orientation (»bending inwards towards the host cell surface«) (Yachou et al. 1999) for the viral envelope gp120 co-receptor binding site V1/V2, the relatively conserved »bridging sheet« (that lies between the protruding and variable V1/V2 and V3 loops) and V3, to achieve optimal co-receptor binding (Rizzuto et al. 1998; Hartley et al. 2005). The co-receptor binding site on gp120 is not usually fully exposed until the primary CD4 receptor is bound.

The V3 loop has been known to be a major determinant of cell tropism and presently of co-receptor use. Positively charged amino acids in V3 that confer a syncytium inducing (SI) phenotype correlate with CXCR4 use. The role of the V1/V2 loops are less clear in the co-receptor interaction but when present V1 and V2 influence both cell tropism and co-receptors used.

Chemokine receptors of CCR5 on the surface of CD4 T cells and macrophages form rods in the cell membrane with a central pore surrounded by the seven transmembrane regions. Four domains are exposed on the cell surface: the N terminus and three extracellular loops E1, E2, and E3. Two sites on co-receptors centered around the N terminus and E2 are involved in HIV entry (Wu et al. 1997; Dragic 2001; Dragic et al. 1998). Sites in the V1/V2 loop, the bridging sheet and V3 loop on the viral envelope gp120, may contribute to at least two specific interactions with co-receptors centered on the N terminus and E2.

Interaction and binding of the virus with the co-receptors accomplishes the second step for virus entry into the host cell.

Fusion of the Virus into the Host (Target) Cell

Interaction and binding of the virus with the co-receptors allow for a more stable, two-pronged attachment between trimeric viral envelope gp120, with host cell CD4 primary receptors and adjacent co-receptors; an action, which, consequently exposes the inaccessible in the naïve state peptide gp41 (Gallaher et al. 1987; Chan et al. 1997; Weissenhorn et al. 1997). This positioning state triggers conformational changes in gp41 subunit allowing the N-terminal fusion peptide gp41 to penetrate the cell membrane as if a signal to »harpoon« the host cell has been given, leading to insertion of its N-terminal fusion peptide into the host cell's membrane (Kowalski et al. 1987; Moore et al. 1991; Sattentau et al. 1991; Carr et al. 1993; Weissenhorn et al. 1997: Furuta et al. 1998).

The HIV-1 gp41 envelope glycoprotein consists of an ectodomain (extracellular), a transmembrane, and an endodomain (intracellular), respectively. The ectodomain contains three major functional regions consisting of a fusion peptide at the amino-terminus of gp41, and two 4-3 heptad repeats (HR) adjacent to the N- (HR1) and C- (HR2) terminal portions of the ectodomain respectively, also called gp41 alpha-helical domains HR1 and HR2 (Gallaher et al. 1989).

Repeat sequences in gp41, HR1 and HR2 then intramolecularly interact between the C- and N-terminal peptide regions of gp41, causing the collapse of the extracellular portion of gp41 and leading to a trimer of hairpins and the formation of coiled-coil (loop) structures (Gallaher et al. 1989; Fass et al. 1996; Chan et al. 1997). Juxtaposition of the host cell and viral

membranes with coiled-coil (loop) structures permeating the cell membrane (resembling to viral particle and host cell membranes being stitched together at places initially) allow fusion of the membranes and subsequent entry of the viral capsid into the host cell.

Fusion of the virus and host cell membranes, leading to the release of the HIV-1 core into the host cell, accomplishes the third and final step of HIV entry into the host cell; the replication process of HIV in the host cell begins!

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