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Interactions of Infectious HIV-1 Virions with Erythrocytes: Implications for HIV-1 Pathogenesis and Infectivity

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1. Introduction

According to widely held current paradigms of cellular infection and transmission of HIV-1 the virus first binds to a membrane receptor on a target cell, such as CD4 and a chemokine receptor (CCR5 or CXCR4) that serve as co-receptors. After penetration of the plasma membrane of the cell by the virus via receptor-mediated fusion, followed by insertion of the viral RNA and intracellular replication, the newly assembled virion buds from the host cell into the extracellular environment where it becomes a cell-free infectious virion. In accordance with this, it is widely believed that prior to infecting new target cells HIV-1 in blood exists mainly as cell-free infectious virions (Ho et al., 1989; Pan et al., 1993). Upon encountering a new target cell a new cycle leads to entry and infection of the new cell. In this chapter, we will review an alternative concept that HIV-1 can bind to human erythrocytes, and that erythrocyte-bound HIV-1 remains infectious and promotes *trans* infection of CD4(+) T cells. We further propose the general concept that is likely that virtually all infectious HIV-1 particles in blood are bound to circulating cells *in vivo*, rather than existing as cell-free circulating virus. We will review various mechanisms that might be involved in binding of infectious HIV-1 to erythrocytes, and the implications that *trans* infection by erythrocyte-bound HIV-1 might have for pathogenesis of HIV-1 and for vaccine development.

2. Binding of HIV-1 to erythrocytes: *In vitro* studies

Several studies have addressed the adherence of HIV-1 to erythrocytes *in vitro*. Olinger et al. (2000) suggested that HIV-1 binding to the surface of CD4(-) cells might be an important route for infection of T cells based on the ability of HIV-1 strain MN (T-cell line-adapted) and X4 and R5 primary isolates to bind to various cell types. Virus apparently bound *in vitro* both to isolated CD4(+) and CD4(-) cells, including peripheral blood mononuclear cells (PBMC), neutrophils, tonsillar mononuclear cells, platelets, and erythrocytes. Virus that had bound to CD4(-) cells was up to 17 times more infectious for T cells in co-cultures than was the same amount of cell-free virus. Enhanced infection of T cells by virus bound to CD4(-)

cells was not due to stimulatory signals provided by CD4(-) cells or infection of CD4(-) cells, and it was proposed that virus bound to the surface of CD4(-) cells was efficiently passed to CD4(+) T cells during cell-cell adhesion. Although the study by Olinger et al. (2000) did not investigate the mechanism of HIV-1 binding or the binding site on the CD4(-) cells, it was suggested that HIV-1 binds at relatively high levels to CD4(-) cells, including erythrocytes, and that cell-bound HIV-1 is highly infectious for T cells.

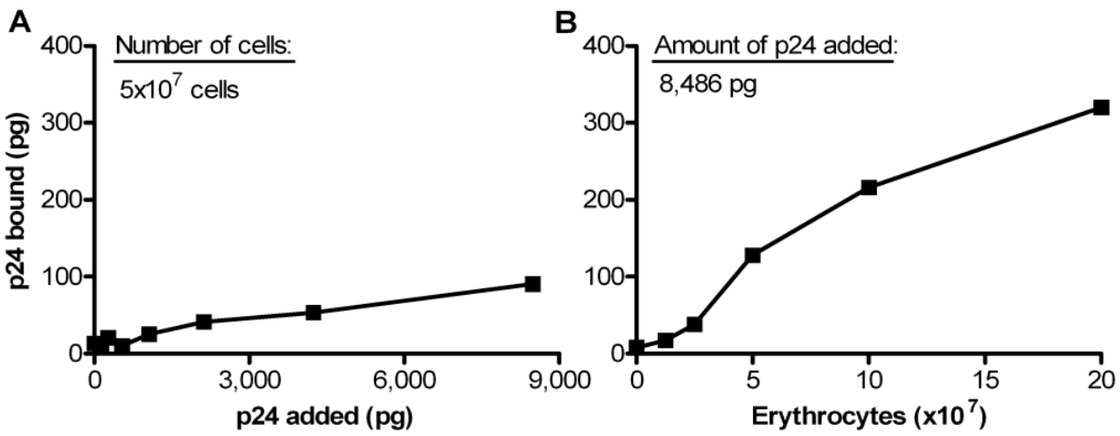

Fig. 1. Binding of a HIV-1 isolate to erythrocytes.

(A) Increasing amounts of HIV-1 isolate 90US_873 (as quantified by p24) were incubated with 5x107 erythrocytes and binding of p24 to the cells was determined. (B) Dose-dependent binding of the HIV-1 isolate (8,486 pg p24) with increasing numbers of erythrocytes. The experiment shown is representative of 3 separate experiments. In each experiment HIV-1 was bound to erythrocytes in triplicate, washed, and the triplicates were pooled for p24 determination. From Beck et al. (2009).

The binding of HIV-1 at 4°C *in vitro* to normal erythrocytes from 30 different individual donors was subsequently confirmed and found to be calcium dependent by Beck et al. (2009), and further confirmed by Garcia et al. (2011). As shown in Fig. 1A, the binding of p24 to 5 x 10^7 erythrocytes obtained from a selected individual donor exhibited a dose-response up to 8,486 pg of added p24 (the maximum amount of p24 in the HIV-1 stock that could be used in the assay); however when this latter amount of p24 was then incubated with increased numbers of erythrocytes, to a level of 20 x 10^7 (the maximum number of erythrocytes that could be used because of viscosity restraints in the assay), a further three-fold increase of p24 binding was observed (Fig. 1B) (Beck et al., 2009). At the highest ratio of erythrocytes/p24 there was no clear plateau in the amount of p24 binding, but it did appear likely that the binding pattern was in the form of a wide and relatively shallow sigmoid curve that might be approaching a plateau.

When the erythrocytes from 30 donors were examined, a mean of only 2.4% of the total added HIV-1 p24 was bound to the erythrocytes, but additional experiments further demonstrated that adsorption of the original HIV-1 preparation with erythrocytes removed essentially all (up to 97%) of the infectivity of HIV-1 for *trans* infection of CD4(+) PBMC (Beck et al., 2009). It was thus demonstrated that only a small fraction of the originally added p24 became bound to the erythrocytes, but this amount comprised virtually all of the infectious HIV-1 particles in the original preparation added to the cells.

From the data shown in Fig. 1 it seems clear that either the binding affinity of infectious HIV-1 particles for erythrocytes is extremely low, or the number of cells in the erythrocyte population that actually bind infectious HIV-1 particles is a very small number of the total cells present. However, because the binding to the cells survived several relatively vigorous washing techniques resulting in a p24-free supernatant, it would appear unlikely that the binding affinity to the cells was low. To estimate the approximate fraction of cells in the erythrocyte population that had the capacity to bind infectious HIV-1 particles, the following theoretical calculations can be considered. If one assumes that: (A) one infectious virion contains ~5,000 molecules of gag p24 (Briggs et al., 2004); and (B) the molecular weight of p24 is 24,000, then there are ~5,000 viruses per pg of p24. If one further assumes (C) that all of the infectious virions that were added to the erythrocytes were contained within 320 pg of p24 that were attached to 20 x 10^7 erythrocytes (Fig. 1B), then the calculation suggests that only approximately 1 infectious virion was bound per 125 erythrocytes. The data thus suggested that the binding of infectious HIV-1 particles to cells in the erythrocyte preparation was a relatively rare event, and perhaps fewer than 1% of the cells that were present in the erythrocyte pool had the capacity to bind HIV-1. However, it was also likely that binding to erythrocytes *per se* did occur because substantial binding was observed with erythrocyte ghosts prepared after the initial binding event was completed. Furthermore, binding was also observed directly with fresh erythrocyte ghosts (Beck et al., 2009).

2.1 Contaminating cell types as potential targets for binding of HIV-1 in erythrocyte preparations

Because <1% of the cells in the erythrocyte population appeared to bind the HIV-1, several possible circulating cell types could be suggested as candidates that might contain the observed HIV-1 binding site, including: myeloid-derived multipotent progenitor cells and long-lived hematopoietic stem cells (Carter et al., 2010; Carter et al., 2011); young erythrocytes or direct precursors of erythrocytes (such as reticulocytes); damaged but still circulating mature erythrocytes; aged erythrocytes near or at the end of their circulating life-span; and CD4(-) nucleated cells that were not removed during the preparation of the erythrocytes.

It is notable that platelets contain two C-type lectins, C-type lectin-like receptor 2 (CLEC-2) and dendritic cell-specific, ICAM-3 grabbing, nonintegrin (DC-SIGN), that are each surface-expressed proteins that exhibit calcium-dependent binding of infectious HIV-1 particles (Boukour et al., 2006; Chaipan et al., 2006; Flaujac et al., 2010). Although it has been suggested that platelets might represent a circulating reservoir for HIV-1, it has also been reported that internalization of HIV-1 by platelets might cause disrupt viral integrity (Boukour et al., 2006; Flaujac et al., 2010). Because platelets are notoriously sticky, it is possible that clumps of platelets might become bound as contaminants on a small number of erythrocytes either *in vitro* or *in vivo*, and because of the ability of platelets to bind HIV-1 these erythrocyte-platelet combinations might then serve as platforms for *trans* infection by attached HIV-1.

Hemolysis of the erythrocytes after the initial binding of HIV-1, followed by centrifugation to remove nucleated cells, revealed that a substantial amount of binding of p24 was found not only on the erythrocyte ghosts, but also on the small number of nucleated cells that contaminated the erythrocyte pool (Beck et al., 2009). Flow cytometry analysis of the erythrocyte population revealed only approximately 0.4% contamination by nucleated (non-

hemolyzed) cells [0.07% CD4(+) and 0.33% CD4(-) cells]. However, based on the small numbers of nucleated cells in the erythrocyte population but the relatively high level of p24 binding to cells other than erythrocytes, it appeared that the binding of HIV-1 to leukocytes was stronger than binding of the HIV-1 to erythrocytes. Despite this, it was further demonstrated that when the initial incubation temperature of 4°C that was used for binding to erythrocytes was subsequently raised to 37°C, no detectable internalization of virus occurred over a period of 4 hours. Binding of p24 at 4°C, or even after 4 hours at 37°C, was substantially eliminated by treatment of the erythrocytes with EDTA. It was thus concluded that binding of the virus to sites on contaminating cells in the erythrocyte population that could be infected by HIV-1 did not account for any of the observed binding of HIV-1 (Beck et al., 2009).

3. Candidate binding sites on erythrocytes

The binding site (or sites) for infectious HIV-1 on erythrocytes, whether protein, carbohydrate, or lipid (including glycolipid or phospholipid), or combinations of these, have not yet been completely determined. In considering this problem, there is also the theoretical and practical difficulty of differentiating the binding of whole infectious virions from binding of defective virus particles or degradation products such as free p24.

The external cell membrane contains numerous proteins with many functions, and the literature on red cell proteins and their functions has been extensively reviewed (Anstee, 2011; Daniels, 2007; Denomme, 2004; Mohandas & Narla, 2005; Reid & Mohandas, 2004; Telen, 2005). At least 60 different erythrocytic surface proteins that could be candidates for binding of HIV-1 are classifiable into at least six categories based on their functions, namely: enzymes; membrane transporters; receptors; adhesion molecules; blood group antigens; and structural proteins. The functions of some of these proteins are known; in others their function can be assumed from the protein structure or from limited experimental evidence. Some of the proteins carry out only one specific function and some have more than one. Some might be evolutionary relics and may no longer have significant functions. Several membrane transporter glycoproteins are polymorphic, and are blood group antigens (such as Kidd, Gill, Rh, etc.). However other receptors and adhesion molecules have blood group function as well (Duffy, Lu, LW).

In pondering the possible binding sites, it is useful to remember that the complement-independent *in vitro* binding described above (section 2) required calcium, and many integrins or adhesion factors, including molecules in the C-type lectin-like domain superfamily such as DC-SIGN on dendritic cells and platelets, require calcium for binding to carbohydrates (Zelensky & Gready, 2005). The gp41 protein of HIV-1 contains a binding site for calcium that co-locates with a binding site for a glycosphingolipid (Ebenbichler et al., 1996; Yu et al., 2008). It is well-known that erythrocytes contain numerous glycosphingolipids, such as ganglioside GM3 (hematoside) and ceramide trihexoside (CTH or Gb3, also known as P^k blood group antigen) (Suzuki, 2009), and that binding of HIV-1 to these molecules, and to other glycolipids, can occur (Fantini et al., 2002; Alving, et al., 2006; Lund et al., 2009).

The above glycosphingolipids are possible candidate binding sites for HIV-1 on erythrocytes. However, binding to GM3 or Gb, or other glycosphingolipids, might initially seem unlikely because they are relatively small molecules and are hidden under overlying proteins in normal erythrocytes. Because of steric hindrance by overlying proteins they cannot even bind to specific antibodies (Alving, 2006). However, binding of antibodies to

erythrocytic glycosphingolipids readily occurs when the erythrocytes have been damaged by proteolytic enzymes that remove some of the overlying proteins to unmask the underlying glycosphingolipid (Koscielak et al. 1968; Alving, 2006). In view of the observation that <1% of the cells in the *in vitro* erythrocyte population bound HIV-1 (see section 2), it is conceivable that the binding of HIV-1 to erythrocytes occurs to glycosphingolipids that are exposed on the small number of cells that are damaged, or that are at a critical point during the evolution from the reticulocyte stage to mature erythrocytes, or perhaps HIV-1 binds to erythrocytes that are senescent and are about to be removed from circulation.

3.1 Duffy blood group antigen on erythrocytes

The Duffy blood group antigen system was originally described in 1950 based on discovery of an alloantibody against an antigen denoted as Fy(a) in a patient with hemophilia who had received multiple transfusions (Cutbush et al., 1950). The Duffy antigen system consists of multimeric erythrocytic membrane surface proteins composed of different subunits in which glycoprotein D is the major subunit that carries the antigenic determinants as defined by anti-Fy(a), anti-Fy(b) antibodies (Tournamille et al., 1997). The Duffy antigen system achieved considerable prominence when it was discovered that it comprised the erythrocytic receptor site for binding and entry of merozoites of *Plasmodium vivax* and *Plasmodium knowlesi* into erythrocytes (Langhi & Bordin, 2006; Miller et al., 1976). Individuals lacking the Duffy phenotype were also found to be resistant to infection by strains of malaria that bind to Duffy antigen on erythrocytes, thus explaining the remarkable resistance to *P. vivax* malaria that occurs in large areas of West Africa. Because of the subsequent discovery that the Duffy antigen also binds to chemokines, resulting in the binding of cytokines to erythrocytes and endothelial cells and perhaps causing regulation of plasma cytokine levels, this blood group antigen family is now commonly known as the Duffy Antigen Receptor for Chemokines (DARC) (Smolarek et al., 2010). DARC belongs to a family of erythrocyte chemokine receptors that bind to interleukin 8 (IL-8), monocyte chemoattractant protein 1 (MCP-1), and RANTES, but that do not bind macrophage inflammatory protein 1α (MIP-1α) or MIP-1β.

In 1998, it was reported that HIV-1 could bind to DARC on erythrocytes *in vitro* and that erythrocyte-bound DARC could cause infection *in trans* of CD4(+) PBMC (Lachgar et al., 1998). In confirmation of this, based on an *in vitro* experimental study with erythrocytes containing or lacking the DARC phenotype, He et al. proposed that HIV-1 specifically binds to DARC on the surface of erythrocytes at 37°, and that this binding results in the *trans* infection of CD4(+) target cells by transfer of infectious HIV-1 to target cells from erythrocytes (He et al., 2008). Binding of HIV-1 particles to erythrocytes was inhibited by recombinant chemokines such as RANTES, but not by recombinant MIP-1α prior to incubation of the cells with HIV-1. It was suggested that RBCs may function as a reservoir for HIV-1 and it was postulated that DARC might be a receptor for HIV-1 on CD4(-) cell subsets such as neurons or endothelial cells. Although neither of these studies directly measured the binding of HIV-1 to DARC on erythrocytes, they provided evidence of increased infection of CD4(+) target cells when the CD4(+) target cells were co-incubated in the presence of DARC(+) erythrocytes, or co-incubated in the presence of DARC(+) erythrocytes that had been previously incubated with HIV-1 and then washed free of unbound HIV-1. Because this was not observed after co-incubation of HIV-1 with DARC(-) erythrocytes, the data were interpreted as evidence of infection *in trans*. It has recently been

further reported that the HIV-1 strain MN gp120 envelope protein might exhibit sequence similarity to the binding domain of Duffy-binding protein of *P. vivax* (Bolton & Garry, 2011).
The experimental conditions used for the reported binding of HIV-1 to DARC by He et al. (2008) differed from those used by Beck et al. (2009) in at least two ways: the HIV-1 preparation was incubated by He et al. with 10^7 erythrocytes (20-fold fewer than used by Beck et al. (2009)) and the initial incubation with HIV-1 was performed at 37° rather than 4°. He et al. (2008) reported that the DARC(+) erythrocytes caused infection *in trans* with 5- to 12-fold greater efficiency than DARC(−) erythrocytes. The larger number of erythrocytes employed by Beck et al. (2009) might therefore explain the binding of HIV-1 observed in the latter study with erythrocytes that were obtained from all donors, including both DARC(-) and DARC(+) erythrocytes. Although the preponderance of the above indirect evidence for HIV-1 binding to DARC supports the suggestion that DARC might enhance the binding of HIV-1 to erythrocytes, it does not negate other reports that adherence of infectious HIV-1 to erythrocytes can also occur through mechanisms that do not involve binding to DARC.
After the above laboratory demonstration of apparent DARC-dependent transfer of infectious HIV-1 from erythrocytes to CD4(+) target cells, He et al. (2008) further provided a detailed epidemiological survey, and a summary, of previously published genetic distributions of DARC(+) phenotype in different racial groups. Based on this survey, and based on a follow-on natural history study of HIV-1 infection (Kulkarni et al., 2009; Nibbs, 2009), they proposed that increased susceptibility to HIV-1 infection may be related to genetic occurrence of the DARC(+) phenotype, with a survival advantage to absence of the DARC phenotype, among Africans and African-Americans. They further concluded that after Duffy(+) individuals become infected with HIV-1 they had a decreased risk of disease progression (see editorial by Walton & Rowland-Jones, 2008).
The epidemiological conclusions that suggested racial predispositions to increased HIV-1 infection or decreased HIV-1 susceptibility among Africans and African-Americans were based on extrapolation from *in vitro* studies, and they caused considerable dissent from these concepts from numerous scientists engaged in large HIV research programs in which infectious patterns among Africans and African-Americans were being examined in detail (Horne et al., 2009; Julg et al., 2009; Walley et al., 2009; Winkler et al., 2009). This controversy relating to epidemiology of HIV-1 infection is interesting and still ongoing, but it is beyond the scope of the present discussion of the occurrence of binding of infectious HIV-1 particles to erythrocytes. At this time, the relative epidemiological importance from a practical standpoint of HIV-1 binding to erythrocytes having DARC(+)phenotypes is still not clear.

3.2 Complement receptors on erythrocytes

Circulating immune complexes (IC) are normally removed from blood through activation of the complement (C) cascade (Hebert, 1991; Schifferli et al., 1986). When the C cascade is activated by IC the production of C4 and C3b results in the binding of the IC to the C4/C3b receptor, also known as complement receptor type 1 (CR1 or CD35), that is present on the surface of the erythrocytes. The erythrocytes then transport the IC to fixed macrophages in the liver and spleen for removal from the circulation.
Complement-mediated binding of pathogen IC to erythrocytes is also well known, and the same mechanisms for removal of the pathogens take place. In the course of HIV-1 infection circulating IC inevitably appear that consist of induced antibodies that are bound to infectious HIV-1 particles (Morrow et al., 1986). Many authors have analyzed the role of C in HIV-1 infection (Aasa-Chapman et al., 2005; Beck et al., 2008; Gras et al., 1997; Huber &

Trkola, 2007; Legendre et al., 1996; Moir et al., 2000; Montefiori, 1997; Stoiber et al., 1997) and direct *in vitro* binding of HIV-1-erythrocyte IC to CR1 on erythrocytes, and even to recombinant CR1, has been demonstrated (Montefiori et al., 1994; Stoiber et al., 2008; Zhou & Montefiori, 1996)

To illustrate C-dependent binding of HIV-1-IC to erythrocytes, Horakova et al (2004). used radiolabeled HIV-1, and also prepared preformed HIV-1/anti-HIV-1 immune complexes (HIV-IC) that were opsonized in various human sera. The HIV-IC were purified using sucrose density gradient ultracentrifugation, and incubated with human erythrocytes. They observed immune adherence of the complexes to erythrocytes, and adherence was abolished when C was blocked. C-deficient sera indicated that both the classical and alternative pathways of C activation played a role. No adherence was seen in C1q-deficient serum, and the adherence of HIV-1 was reduced when the alternative pathway was blocked using anti-factor D Abs. The adherence could be inhibited by a mAb against CR1. At supraphysiological concentrations, purified C1q mediated the binding of a small fraction of HIV-1 and HIV-IC to erythrocytes.

4. Implications of binding of HIV-1 to erythrocytes for HIV-1 pathogenesis and vaccine development

The immune system serves as the primary defense against infection by pathogenic microorganisms. In the quest for development of an HIV-1 vaccine it is believed that neutralizing antibodies may be a useful, or even vital, requirement (Mascola & Montefiori, 2010). In addition, innate functions initiated by antibodies, including antibody-dependent complement activation, and Fc-receptor mediated antibody-dependent cell-mediated cytotoxicity (ADCC) or antibody-dependent cell-mediated viral inhibition (ADCVI) may also be mobilized, even by non-neutralizing antibodies (Asmal et al., 2011; Forthal & Moog, 2009). In the present context, the question arises whether erythrocytes may serve as an immunologically protected site for infectious HIV-1 virions that can cause HIV-1 infection of infection of HIV-1-susceptible cells *in trans*. To address the above question, Beck et al. (2011) studied the ability of two well-known broadly neutralizing human monoclonal IgG antibodies (mAbs), 4E10 and b12, to prevent *trans* infection of CD4(+) PBMC by erythrocyte-bound HIV-1 both in the presence and absence of complement (Fig. 2).

In the absence of C both of the mAbs neutralized *trans* infection of erythrocyte-bound virus less effectively than neutralization of cell-free virus, and at a low concentration 4E10 even caused enhanced *trans* infection, perhaps because of Fc-receptor mediated uptake of the virus by the PBMC. However, when cell-free HIV-1 was incubated with the 4E10 mAb in the presence of C, followed by incubation with erythrocytes, significant enhancement of *trans* infection occurred (Fig. 2). In contrast, if the HIV-1 was first pre-incubated with erythrocytes, and the 4E10 mAb and C were then added later, significant inhibition of *trans* infection was observed (Fig. 2).

The explanation for these different effects of C was explained by Beck et al. (2011) as being determined by different binding sites for HIV-1 on the erythrocyte. As illustrated in Fig. 3B, when cell-free HIV-1 was exposed to 4E10 and C, partial activation of the C cascade occurred and C3b was generated, as a result of which the viable infectious HIV-1 became bound to CR1 on the erythrocytes, leading to *trans* infection of PBMC. In contrast, as shown in Fig. 3A, when the HIV-1 was pre-attached to erythrocytes (presumably to a site other than CR1), then subsequent exposure to 4E10 and C caused complete activation of C, leading to

generation of membrane attack complexes and killing of the HIV-1. Interestingly, the b12 mAb exhibited no C-dependent effects on erythrocyte-bound HIV-1, an observation that was compatible with previous absence of observed C effects in attempts to use b12 to inhibit mucosal infection in macaques.

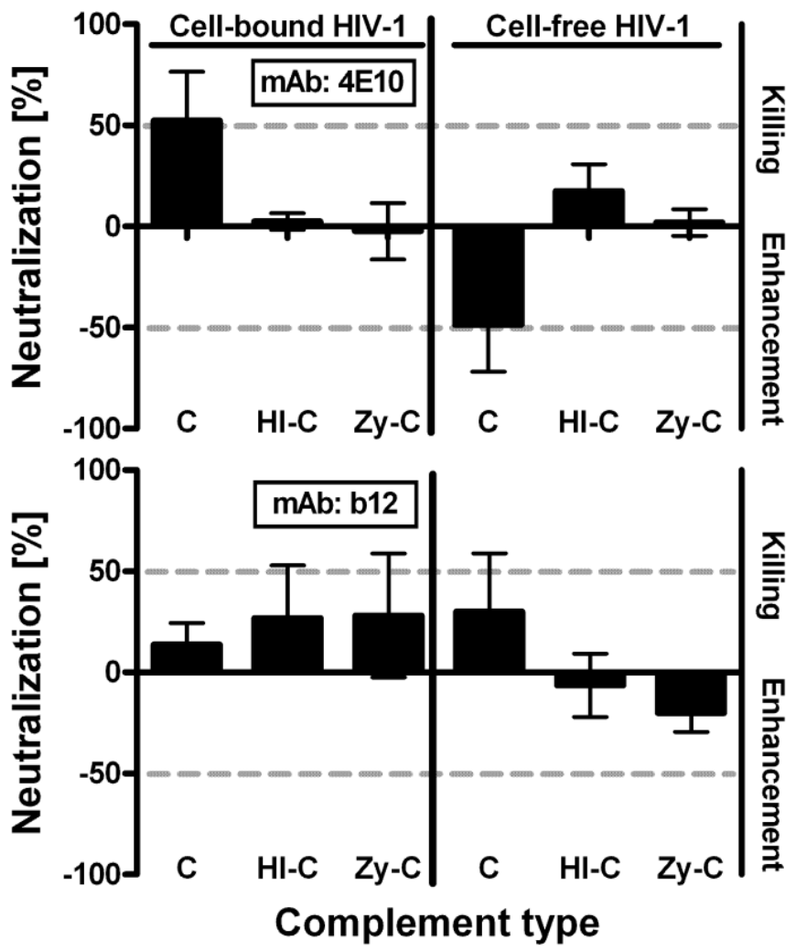

Fig. 2. Effects of antibody-dependent C activation on the trans infection of PBMC by erythrocyte-bound HIV-1-mAb complexes.

(A) Data with 4E10 are the mean±SEM of 8 experiments. (B) Data with b12 are the mean ± SEM of 6 experiments . The baselines represent the values obtained in the absence of C, heat-inactivated C (HI-C), or C inactivated by treatment with zymosan. (Zy-C). The dashed lines indicate the levels of 50% or−50%, defined as positive cutoffs for inhibition or enhancement of virus growth, respectively. In each case, 4E10 had been pre-incubated with the cell-bound or cell-free HIV-1, followed by addition of C, HI-C, or Zy-C, as indicated. From Beck et al. (2011).

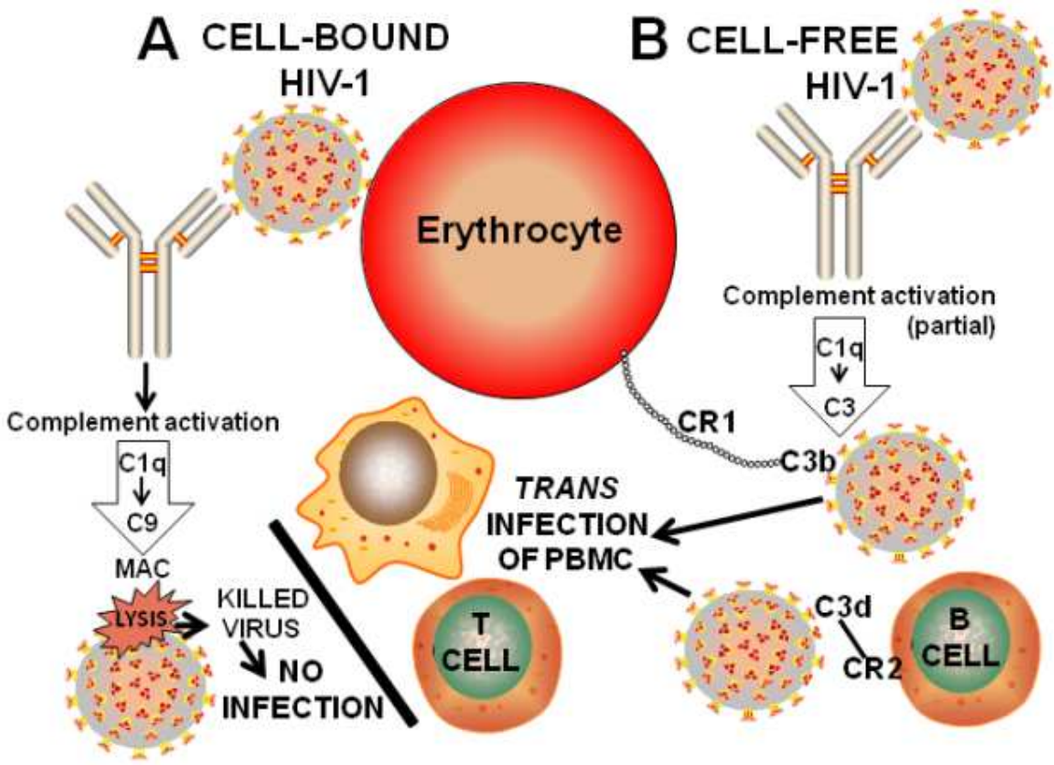

Fig. 3. Schematic representation of C-dependent neutralization of erythrocyte-bound virus, and C-dependent enhancement of infection of PBMC by cell-free virus.

(A) After antibody-independent and C-independent binding of HIV-1 to erythrocytes (Beck et al., 2009), binding of 4E10 (Fig. 4A), but not b12 (Fig. 4B), to the erythrocyte-bound HIV-1 results in C-dependent neutralization. (B) Binding of 4E10 (Fig. 4A), but not b12 (Fig. 4B), to cell-free HIV-1 results in C-dependent binding to CR1 on erythrocytes or B cells, or CR2 on B cells, with enhanced infection of PBMC through trans infection of PBMC by erythrocyte-bound or B cell-bound HIV-1. From Beck et al. (2011).

The conclusions by Beck et al. (2011) were that antibodies and C each represents a two-edged sword. Under certain circumstances, and depending on the individual antibody, inhibition or enhancement of *trans* infection of PBMC can be caused either by the antibody itself or by innate mediators such as Fc receptor binding or activation of C.

5. Does HIV-1 bind to erythrocytes *in vivo*?

In view of the considerable *in vitro* evidence that HIV-1 can bind to erythrocytes, the question naturally arises whether HIV-1 actually binds to erythrocytes *in vivo*. Three reports have examined whether HIV-1, or markers of the presence of HIV-1, can be detected on erythrocytes obtained from infected individuals. In the first study, Hess and colleagues reported that infectious HIV-1 was bound to erythrocytes via immune complexes (Hess et al., 2002; Levy, 2002). Hess et al. showed that HIV-1 RNA and infectious virus was bound to erythrocytes circulating in blood of HIV-1-infected patients. Even in infected individuals who lacked detectable plasma HIV-1 RNA, erythrocyte-associated HIV-1 was readily

detected. They concluded that viral RNA was bound to immune complexes with a short half-life.

In a second study more highly purified erythrocytes were used from 13 HIV-1 infected but aviremic patients, 11 of whom were receiving ART and 2 of whom were "long-term nonprogressors" who were not receiving ART (Fierer et al., 2007). In this study, that used PCR detection techniques, the previous conclusions of Hess et al. (2002) were disputed in that virus was not detected on the purified erythrocytes (Fierer et al., 2007). Although the reason for the discrepancy with the previous study is unclear, Fierer et al. (2007) suggested that the previously studied cell population of Hess et al. (2002) might have contained a higher level of contaminating CD4(+) lymphocytes that were removed by Fierer et al by using more stringent purification techniques.

In a third recent study, the presence of p24-antigen bound to highly purified erythrocytes from HIV-1-positive individuals was reported (Garcia et al., 2011). In this study 51 out of the 71 patients with detectable plasma viral loads (pVL) showed erythrocyte-associated p24-antigen (Ag-E) whereas 13 showed p24-antigen in plasma (Ag-P). Twenty-two out of the 51 patients with Ag-E showed high pVL and undetectable Ag-P. The amount of erythrocyte-associated p24-antigen was not related to p24-antigen in plasma or pVL levels. Among the 41 patients with prior undetectable pVL, eight presented detectable pVL and erythrocyte-associated p24-antigen at the moment of the study. The other 33 showed undetectable pVL and 5 of these presented erythrocyte-associated p24-antigen. A positive relationship was found between the presence of erythrocyte-associated p24-antigen and the detectable pVL. This study thus confirmed the presence of erythrocyte-associated p24-antigen in HIV-1-infected individuals. Since erythrocyte-associated p24-antigen is not always related to pVL or p24-antigen in plasma, erythrocyte associated p24-antigen showed viral expression not represented in plasma.

Although the above three studies suggest that some degree of controversy exists, the preponderance of data now indicates that HIV-1 does bind to erythrocytes *in vivo*. In view of this it is reasonable to speculate whether such binding might result in hematologic abnormalities in HIV-1-infected patients. Changes in erythrocyte and lymphocyte membrane properties have been associated with infection, including changes in calcium signaling, decreased membrane fluidity, decreased acetylcholinesterase activity, and decreased intracellular calcium concentration (Martins-Silva et al., 2006). It was concluded that the observed changes were consistent with the hypothesis that erythrocytes were being maintained as a circulating *in vivo* reservoir of infectious virus and that this was causing adverse physical changes in the erythrocytes. Regardless of the exact mechanism(s) involved in causing these effects, it is apparent that anemia might be a potential sequel.

Anemia is reportedly the most common hematologic manifestation of HIV-1 infection (Claster, 2002). However, there can be multiple causes of anemia, including reduced erythrocyte production. As noted earlier (section 2.1), HIV-1 infects multipotent progenitor cells in the bone marrow that might affect reticulocyte production (Carter, et al., 2010). Anemia might also be secondary to a variety of causes such as drug-related anemia, parvovirus infection, and nutritional deficiencies, in addition to increased erythrocyte destruction. Clearly, appropriate therapies can address the various correctable causes of the clinical course of anemia. However, it should be noted that regardless of the underlying cause, anemia has been cited as an independent predictor of mortality and progress of disease among HIV-1-infected women in Tanzania (O'Brien et al., 2005).

6. Conclusion

From the above three studies it is evident that the question of HIV-1 binding to erythrocytes *in vivo* has generated some degree of controversy. Although the reasons for the failure of Fierer et al. (2007) to detect erythrocyte-bound HIV-1 are unknown, in view of the study by Hess et al., 2002 and the confirmatory results of Garcia et al. (2011), and when this it taken in the context of the several studies that have demonstrated binding of HIV-1 to erythrocytes *in vitro*, it seems likely that infectious HIV-1 virions are present on circulating erythrocytes in HIV-1 infected persons. In view of the recent *in vitro* evidence by Beck et al. (2011) that erythrocyte-bound HIV-1 may sometimes be more difficult to neutralize with antibodies than cell-free HIV-1, and that both inhibition and enhancement can occur with antibody-mediated innate immunity in the presence of C, it also seems likely that circulating erythrocytes may represent an attachment site for infectious HIV-1 that is relatively protected from attack by antibodies and C. It is possible that further research will identify means to induce antibodies that block *trans* infection by erythrocyte-bound HIV-1. A corollary of this is that development of a *trans* infection neutralization assay may also be useful as an *in vitro* correlate of protective immunity in addition to neutralization assays in which cell-free virus is the infecting agent.

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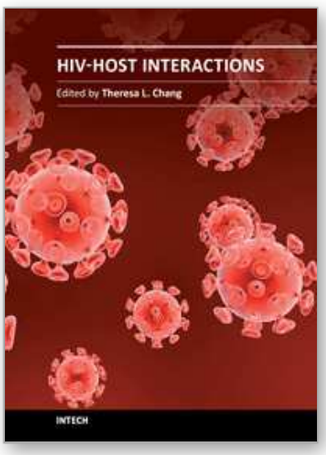

HIV-Host Interactions

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HIV remains the major global health threat, and neither vaccine nor cure is available. Increasing our knowledge on HIV infection will help overcome the challenge of HIV/AIDS. This book covers several aspects of HIV-host interactions in vitro and in vivo. The first section covers the interaction between cellular components and HIV proteins, Integrase, Tat, and Nef. It also discusses the clinical relevance of HIV superinfection. The next two chapters focus on the role of innate immunity including dendritic cells and defensins in HIV infection followed by the section on the impact of host factors on HIV pathogenesis. The section of co-infection includes the impact of Human herpesvirus 6 and Trichomonas vaginalis on HIV infection. The final section focuses on generation of HIV molecular clones that can be used in macaques and the potential use of cotton rats for HIV studies.

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