Contents lists available at ScienceDirect

ASHI
AMERICAN SOCIETY FOR
HISTOCOMPATIBILITY &
IMMUNOGENETICS
www.ashi-hla.org

journal homepage: www.elsevier.com/locate/humimm

Human
Immunology

Role of DC-SIGN and L-SIGN receptors in HIV-1 vertical transmission

Ronaldo Celerino da Silva [a,b], Ludovica Segat [c,*], Sergio Crovella [a,c]

[a] Department of Genetics, Federal University of Pernambuco, Cidade Universitária, Recife, PE, Brazil
[b] Laboratory of Immunopathology Keizo Asami, Federal University of Pernambuco, Cidade Universitária, Recife, PE, Brazil
[c] Genetic Service, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Burlo Garofolo, Trieste, Italy

ARTICLE INFO

ABSTRACT

The innate immune system acts in the first line of host defense against pathogens. One of the mechanisms used involves the early recognition and uptake of microbes by host professional phagocytes, through pattern recognition receptors (PRRs). These PRRs bind to conserved microbial ligands expressed by pathogens and initiate both innate and adaptive immune responses. Some PRRs located on the surface of dendritic cells (DCs) and other cells seem to play an important role in human immunodeficiency virus type 1 (HIV-1) transmission. Dendritic cell–specific intercellular adhesion molecule–3 grabbing non-integrin, CD209 (DC-SIGN) and its homolog, DC-SIGN-related (DC-SIGNR or L-SIGN) receptors are PPRs able to bind the HIV-1 gp120 envelope protein and, because alterations in their expression patterns also occur, they might play a role in both horizontal and vertical transmission as well as in disseminating the virus within the host. This review aims to explore the involvement of the DC-SIGN and L-SIGN receptors in HIV-1 transmission from mother to child.

© 2011 American Society for Histocompatibility and Immunogenetics. Published by Elsevier Inc.

1. Introduction

The Joint United Nations Program on HIV-1/AIDS estimates that 2.1 million children worldwide are infected with human immunodeficiency virus type 1 (HIV-1) [1] and that more than 430,000 children were newly infected in 2008. Mother-to-child transmission, also known as vertical transmission, accounts for more than 40% of all HIV-1 infections in children [2] and can occur in three ways [3–5]: during pregnancy through the placenta (transplacental or intrauterine transmission); during delivery (intrapartum transmission) through amniotic fluids, infected blood and cervical secretions; and during the process of breastfeeding. In addition, some independent factors have been associated with vertical transmission of HIV-1, such as high maternal viral load, low amount of CD4$^+$ T cells, vaginal delivery and lower gestational age [4,5].

Global estimates show that, without specific medication, the rate of transmission of HIV-1 from mother to child is around 15–45% [6]; using antiretroviral therapies, this percentage has sharply dropped to 2%. However, although prophylactic antiretroviral therapy can reduce mother-to-child transmission to 2%, the limited access to timely diagnosis and drugs in many developing countries reduces the potential impact of this strategy [5]. Despite the sharp fall in the rate of viral transmission, a significant percentage of children are still being infected with HIV-1; the mechanisms used by the virus to escape the immune response and infect targets cells of children born to infected mothers treated with antiretroviral therapies still remain to be clarified.

A better understanding of the immunologic mechanisms acting at the maternal–fetal interface and of host–pathogen interaction is essential for the development of alternative interventions aimed to prevent viral transmission. This review aims to explore the involvement of the dendritic cell–specific intercellular adhesion molecule–3 grabbing non-integrin, CD209 (DC-SIGN) and DC-SIGN-related C-type lectin domain family 4, member M (L-SIGN) receptors in HIV-1 transmission from mother to child.

2. DC-SIGN and L-SIGN receptors

The innate immune system is the first line of host defense against pathogens; it involves the early recognition and uptake of microbes by host professional phagocytes, such as dendritic cells (DCs) and macrophages, through germline-encoded receptors, known as pattern recognition receptors (PRRs) [7]. These proteins bind to conserved microbial ligands expressed by the pathogens, and initiate both innate and adaptive immune responses. PRRs are involved in phagocytosis, and antigen presentation could activate intracellular signaling and cytokine secretion. The efficiency of this initial pathogen recognition may have important consequences in the pathogenesis of infectious diseases [8].

Some PRRs located on the surface of DCs and other cells seem to play an important role in HIV-1 transmission. Of particular interest are the DC-SIGN and its close relative, L-SIGN (also known as DC-SIGN related [DC-SIGNR], CD209L or CLEC4M) receptors [9,10].

* Corresponding author.
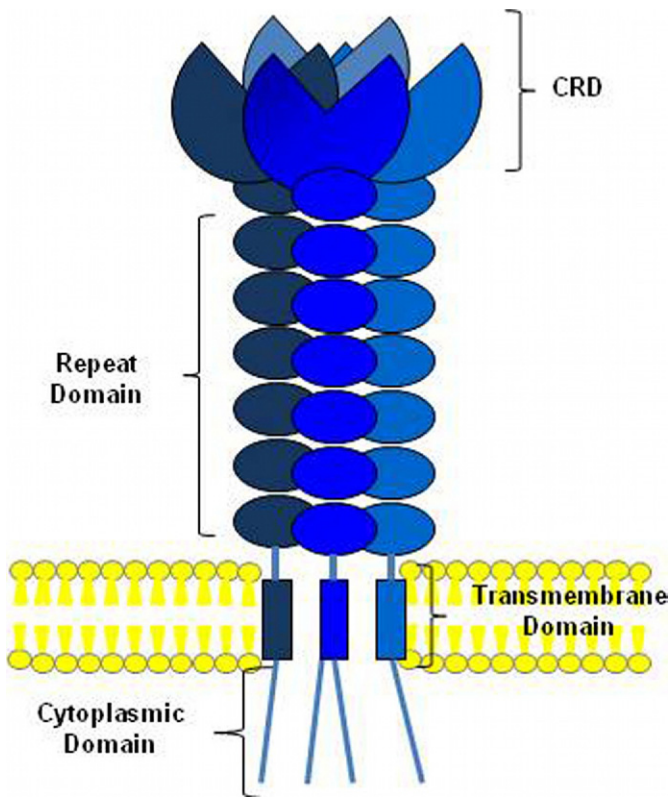 E-mail address: segat@burlo.trieste.it (L. Segat).

Fig. 1. Predicted protein domains in DC-SIGN and L-SIGN.

DC-SIGN and L-SIGN receptors, two C-type lectins, are long type II integral membrane proteins [11,12] that are involved in both innate and adaptive immunity [13–15]. They present strong dependence on calcium and act as cellular adhesion's receptors and are involved in pathogen recognition [16,17]. As pathogen-recognition receptors, both these lectins recognize a wide range of microorganisms, some of which have a major impact on public health. For example, DC-SIGN captures viruses, such as Ebola virus [18], hepatitis C virus [19,20], Dengue virus [21], cytomegalovirus [22], and SARS coronavirus (SARS-CoV) [23,24], bacteria such as *Mycobacterium tuberculosis* [25] and *Helicobacter pylori* [26], and parasites such as *Leishmania pifanoi* [27]. L-SIGN is able to capture viruses such as Ebola virus [18], hepatitis C virus [19,20,28], and more

recently SARS-CoV [23,29], as well as bacteria such as *M tuberculosis* [30], and *Leishmania infantum* [27]. Both DC-SIGN and L-SIGN can recognize and capture human immunodeficiency virus 1 by binding to the gp120 glycoprotein [31–35].

DC-SIGN and L-SIGN receptors are organized into three structurally distinct regions (Fig. 1): an intracytoplasmatic tail domain responsible for internalization and signal transduction [36] that consists of N-terminal, LL, and YKSL motifs and a triacidic group (EEA), then a transmembrane domain and finally an extracellular domain, which is further divided into two structures, the neck repeat region and the carbohydrate recognition domain (CRD) [17].

The neck repeat region usually consists of 7 full and 1 incomplete tandem repeats of a sequence of 23 highly conserved amino acids, but the number of repeats can vary in the population: the neck repeat region of the L-SIGN receptor is highly polymorphic (4–10 repetitions are often found), while the one of DC-SIGN is less polymorphic (mainly seven repetitions) [12,17,37]. The neck repeats region plays a crucial role in tetramerization and supports carbohydrates' recognition, thus directly influencing the receptor's binding affinity to pathogens [8,17,36].

The number of tandem-neck repeats determines the multimerization status (Fig. 2). Feinberg et al. [38] showed that the lack of two repeats (five-repeat allele) results in partial dissociation of the final tetramer, whereas the lack of even more than five repeats causes a reduction in the overall stability of the molecule. By using a series of recombinant soluble receptors with different number of repeats, Synder et al. [39] showed that the binding affinity to HIV-1 gp120 glycoprotein was affected by the length of the repeats and multimerization status, with tetrameric forms presenting a higher affinity than shorter monomeric forms. The CRD, both in DC-SIGN and L-SIGN, is flexibly connected to the neck repeat region, allowing a departure from the membrane, which enables the binding of pathogens in a calcium-dependent manner [36].

DC-SIGN and L-SIGN belong to the CD209 gene family and probably originated following a gene duplication event [17]. The human genes encoding DC-SIGN and L-SIGN map on 19p13.2-3 and extend approximately for 13 kb [35,40]. In addition, they share the same introns and exons organization (consisting in seven exons and five introns) and the encoded proteins present a high similarity at the amino acid level (77% identity) [17].

The two receptors are characterized by different expression patterns. DC-SIGN is highly expressed in monocytes and CD34+ monocyte-derived DCs and in subsets of immature and mature DCs in various tissues such as dermis, mucosa, spleen, placenta (special-
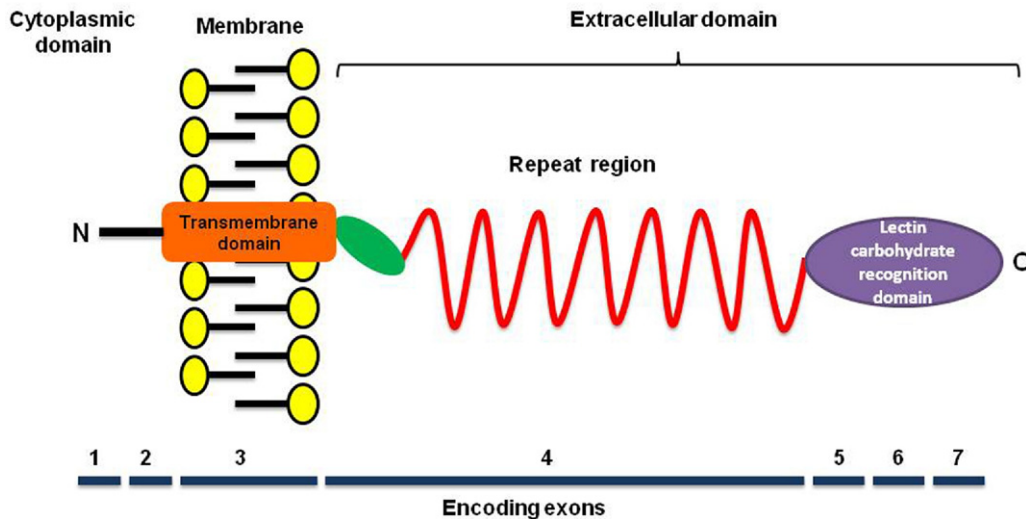

Fig. 2. Schematic representation of tetrameric form of DC-SIGN and L-SIGN. CRD, carbohydrate recognition domain.
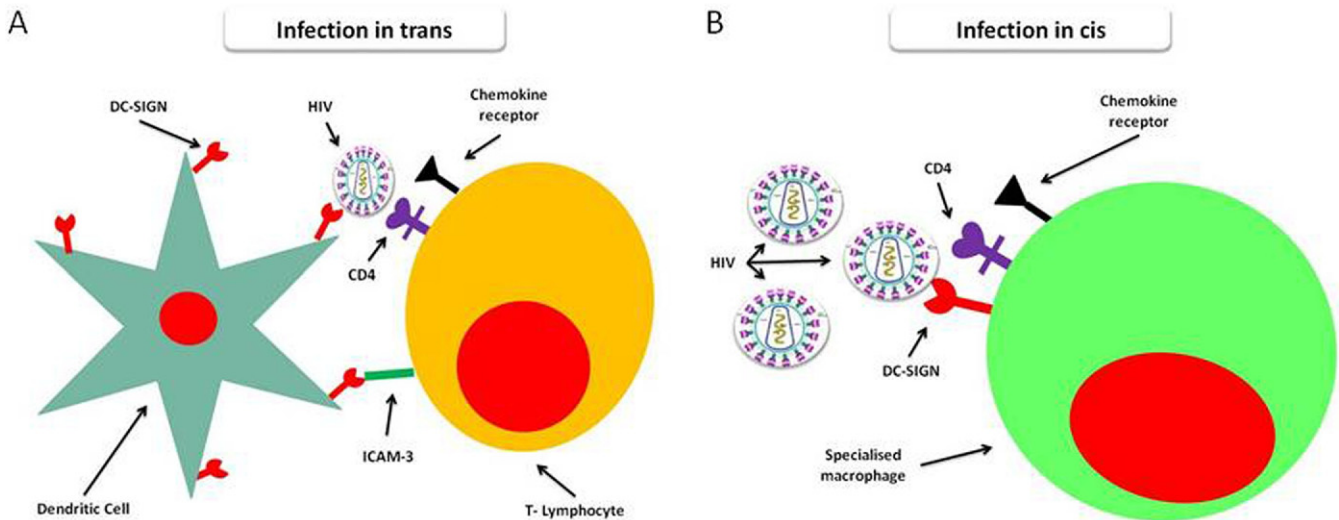
Fig. 3. Paths of infection by HIV-1. (A) Infection *in trans* using DC-SIGN receptor in DCs; this mechanism is very similar to the one used by L-SIGN receptor in endothelial cells. (B) Infection *in cis* using DC-SIGN in specialized macrophage.

ized macrophages of decidua and Hofbauer cells in the chorionic villi), and lung (specialized macrophages in the alveoli) [36,41,42]. In contrast, L-SIGN is not expressed by DCs or monocyte-derived DCs *in vitro*, and its expression is limited to some tissues, such as lymph nodes (endothelial cells in the subcapsular sinus), liver (sinusoidal endothelial cells), placenta (capillary endothelial cells), lung (alveolar cells and endothelial cells), and intestine (villi capillaries in the lamina propria of the terminal ileum, Peyer's patches) [12,36].

3. DC-SIGN and L-SIGN interaction with HIV-1

As a specific adhesion receptor, DC-SIGN mediates the interaction between DCs and T cells by binding with high affinity to ICAM-3 [9,11]. The interaction between DC-SIGN and ICAM-3 expressed on T cells contributes to a close interaction between DCs and T cells required for an efficient antigen presentation. DC-SIGN can also facilitate the capture of viral antigens by class I and class II MHC, leading to activation of specific CD8^{+} and CD4^{+} T cells [36].

The interaction between DC-SIGN and L-SIGN and the HIV-1 has been already well studied [9,16,32–34,36,39,43–49]. As mentioned before, DC-SIGN can bind to the gp120 protein of HIV-1 [41,42,50] capturing the virus and possibly increasing HIV-1 transmission [12]. Similar to DC-SIGN, L-SIGN also captures the HIV-1 virus by binding to the gp120 and promoting the enhancement of T cell infection by HIV-1 *in trans* [17,34]; however, L-SIGN can also internalize the virus and promote virus degradation in a proteasome-dependent manner, possibly directly affecting the outcome of the infection by HIV-1 [5]. The presence of L-SIGN on the surface of endothelial cells in lymph node sinuses represents an obvious mechanism by which the virus can be transmitted to CD4^{+} cells that traffic into lymph nodes via the afferent lymphatics. In addition, since L-SIGN binds to ICAM-3 and may bind to other cell surface receptors, interactions between T-cells and the endothelial cell surface may occur more frequently, increasing the likelihood of virus transmission [9].

Although DC-SIGN and L-SIGN are not direct receptors for HIV-1 infection, they work efficiently in the capture of HIV-1 from the periphery, thus facilitating viral transmission to secondary lymphoid organs rich in T cells and increasing the infection of target CD4^{+} cells [16,32,33].

The HIV-1 virus can infect cells through two different paths: the *trans*- and the *cis*-infection (Fig. 3A, B). Although infection *in trans* occurs when DC-SIGN is expressed on a separate cell from the one

that becomes infected, the infection *in cis* may occur when DC-SIGN is co-expressed with CD4 and chemokine receptor (*e.g.*, CCR5) on a permissive cell type, such as macrophages [16,36,40]. Co-expression of CD4, CCR5, and CXCR4 receptors with DC-SIGN receptor has been blamed for the increase in the efficiency of HIV-1 infection, suggesting the involvement of the DC-SIGN receptor in viral transmission, besides increasing the efficiency of the infection *in cis* [51]. Both DC-SIGN and L-SIGN receptors are involved in HIV-1 infection *in trans* [34]. However, the HIV-1 infection *in cis*, has only been observed so far for DC-SIGN receptor.

The interaction of DC-SIGN and L-SIGN molecules with the HIV-1 occurs through the connection between their CRD with the gp120 viral envelope glycoprotein [16,17]. Binding of the gp120 to DC-SIGN and L-SIGN molecules may induce a conformational change in the gp120 itself that enables a more efficient interaction with CD4 and/or the chemokine receptor and subsequent membrane fusion with T cells. Alternatively, the binding of viral particles to the DCs may increase the probability that entry will occur after binding to the CD4 and co-receptor complex on target cells [10]. The ability of DC-SIGN and L-SIGN receptors to capture and transmit the HIV-1 to T cells may largely depend on their membrane organization in rafts or their capability to multimerize [10]. In addition, alternative splicing events can occur in DC-SIGN e L-SIGN, leading to the production of a vast repertoire of membrane-bound and soluble isoforms, which may also differently affect the process of HIV-1 transmission [5,17,52].

4. DC-SIGN and L-SIGN implications in vertical transmission of HIV-1

4.1. DC-SIGN and L-SIGN in trans-placental HIV-1 transmission

The human placenta is responsible for a close juxtaposition between fetal and maternal blood; however, this apparent barrier is permeable enough to display the HIV-1 from the mother, a fact that leads to fetal exposure to virus [53]. Thus, the placenta can play an important role in the transmission of HIV-1 infection. Most cases of vertical transmission via uterus occur through of the placenta (Fig. 4), especially during the third trimester of pregnancy [43]. It is estimated that the trans-placental or intrauterine HIV-1 transfer comprise 17–38% of cases of vertical transmission, but little is known about the mechanisms involved in the transmission of the virus [54]. Some cell types are pointed out as likely targets for the viral spread, such as macrophages present in the decidua and spe-
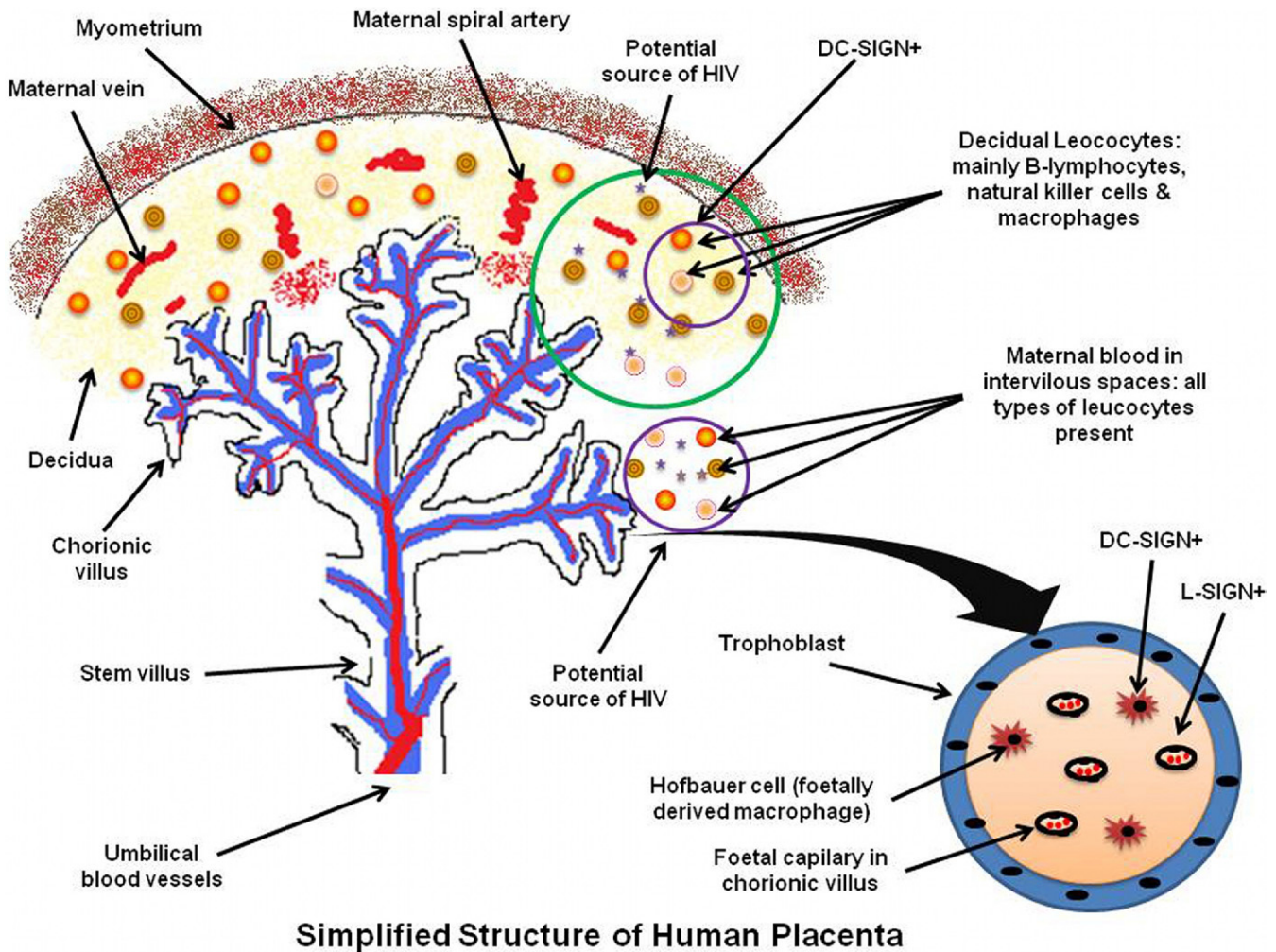
Fig. 4. Schematic summary of placental structure and salient features that may be involved in transplacental transmission of HIV-1. There is an intimate relationship between fetal and maternal tissues in the placenta. Resident leukocyte populations on both the fetal and maternal sides are indicated. DC-SIGN is expressed on fetally derived Hofbauer cells in chorionic villi and on maternally decidual macrophages. These cell populations are in very close proximity. L-SIGN is expressed on placental capillary endothelium.

cialized macrophages present in the placenta (Fig. 4), also known as Hofbauer cells [54]. Both decidual macrophages and Hofbauer cells play important roles in the placental physiology, the firsts promoting the development and control of blood flow and the latter acting in the defense against infectious agents (Hofbauer cells) [54].

Hofbauer cells, specialized macrophages from human placenta, support infection by HIV-1 both *in vitro* and *in vivo* [55]. This ability to support HIV-1 infection is probably associated with the expression of some cellular receptors related to the infection of T lymphocytes, such as CD4, CCR5, CXCR4, and DC-SIGN, also expressed in these cells [54,55]. During pregnancy, there is an increased expression of DC-SIGN by Hofbauer cells in the chorionic villi, and this expression has been correlated with increased rates of HIV-1 vertical transmission [54]. Thus, DC-SIGN can enhance the binding of HIV-1 on the surface of Hofbauer cells, providing an efficient mechanism by which the virus can be transmitted to other receivers permissible to HIV-1 *in trans*. Thus, one can wonder: How is the contact between native virus-bound infected cells with the fetal cells expressing receptors for HIV-1?

The main physical barrier between fetal Hofbauer cells and maternal fluids is the wall of the trophoblast cells; however trophoblast cells can express receptors for HIV-1 entry, so they can be infected by the virus [55]. Moreover, breaches in the wall of the trophoblasts can originate from spontaneous processes or in consequence of infectious diseases (such as corioamniotite) and be-

havioral habits such as smoking and drug use [55,56], allowing a direct contact between fetal Hofbauer cells DC-SIGN$^+$ CD4$^+$ CCR5$^+$ CXCR4$^+$ and viral particles adsorbed to the maternal decidual macrophages or DCs expressing DC-SIGN, present in maternal blood [54,55,57]. Therefore, the contact between maternal and fetal cells through the wall of the trophoblasts, allows the efficient spreading of HIV-1 to fetal cells expressing receptors for viral binding and entry, allowing establishment of the infection [55].

A study has suggested that the mechanism of HIV-1 association with the cells, such as HIV-1 adsorbed to the DC-SIGN receptor, operates more efficiently in pregnancies where the viremia remains low because of the administration of antiretroviral therapies [54]. Why does this happen?

Some authors explain that binding of viral particles to DC-SIGN may focus or concentrate the virus particles at the surface of the DC and may thus increase the probability that entry will occur after binding to the CD4 and co-receptor complex on target cells [9]. In addition, the HIV-1 virus can remain viable for several days on the DC-SIGN– expressing cell, and then can be more efficiently transferred to T cells than to the transfer executed by free cells [10,16]. For the L-SIGN receptor, this fact is not observed. In addition, some authors propose three different mechanisms to explain how the HIV-1 virus is transmitted from mother to child, via the placenta.

The first mechanism suggests that Hofbauer cells infected with HIV-1 or with the virus adsorbed to their cell membrane through

receptors, such as DC-SIGN, may enter the fetus through the umbilical vein [54,55]. The second mechanism is that Hofbauer cell infected by HIV-1 or carrying the virus adsorbed on the surface, remains *in situ* in the chorionic villi, promoting HIV-1 antigen presentation and subsequent T lymphocytes infection. However, this mechanism seems unlikely, since T lymphocytes are inconspicuous in chorionic villi [54,55]. The third mechanism argues that Hofbauer cells may become infected by HIV-1 and may release infectious viral particles, which may become adsorbed to L-SIGN on the immediately adjacent placental capillary endothelium. The endothelium may, in turn, mediate infection of HIV-1 receptor–positive T-lymphocytes circulating in the blood. Infected T lymphocytes or Hofbauer cells either productively infected with HIV-1 or simply with the virus adsorbed to their surface may then travel between the placenta and the fetus in umbilical cord blood [16,54,55].

4.2. DC-SIGN and L-SIGN in post-partum HIV-1 transmission

In the intra- and post-partum vertical transmission of HIV-1, the virus is delivered and transmitted because of the contact with amniotic fluid, maternal blood, and cervical secretion (intra-partum) or with breast milk (post-partum) [3,58].

It has been reported that, in the absence of a prophylactic anti-retroviral therapy, the breast milk of infected mothers is responsible for more than 40% of cases of children infected with HIV-1 via vertical transmission [2–4,59]. Some factors, such as the viral load in the plasma and breast milk may be relevant for vertical transmission of HIV-1 [60].

Transmission of the HIV-1 virus from mother to child via breast milk can occur by free virus particles and/or viral particles associated with cells [4]; in this case, the expression of cellular receptors for recognition and adhesion of pathogens is required. Among the cell types involved in the transmission of HIV-1 via breastfeeding, macrophages and mammary epithelial cells should be mentioned. Breast milk is the only bodily fluid that contains a large number of macrophages, comprising more than 80% of all cells present in colostrum [61]. Expressing CCR5, macrophages are prime targets of the HIV-1 virus, which uses the co-receptors CCR5 for viral entry [4]. In addition, macrophages, derived from peripheral blood monocytes (PBMo), are present in different concentrations throughout lactation, acting as immunoprotective *in situ* [61].

Moreover, it has been reported that macrophages also express DC-SIGN receptors [61]. In certain situations, the expression levels of DC-SIGN on macrophages can be quite high, especially when stimulated with interleukin (IL)– 4, which also promotes reduction in the expression of CCR5 and CXCR4, suggesting the need for changes in local inflammatory Th2 dominance for an acceleration of HIV-1 transmission via breastfeeding [59–61]. Local production of IL-4 during infectious processes, as in mastitis, can over-regulate the expression of DC-SIGN on macrophages, suggesting the association of mastitis with high viral load in breast milk and high risk of vertical transmission of the virus [61].

Along with the macrophages, mammary epithelial cells may also be infected by HIV-1, through the co-receptor CXCR5 [4]. Some studies suggest the possibility of a HIV-1 compartmentalization between blood and milk, suggesting that the virus could be produced in and transmitted by the milk, through the mammary epithelial cells. In this sense, the viruses that derived from mammary epithelial cells can determine the tropism of HIV-1 transmitted to cells located in the gastrointestinal tract [60].

After being introduced in the organism through infected breast milk, the virus reach the mucosa of the upper intestine, where, in the lamina propria, a large pool of lymphocytes expressing CCR5 and CXCR4 facilitate viral replication. The presence of DCs expressing a series of receptors, such as CD4/CCR5, DC-SIGN, and DC206,

has been reported in the human gut [58]. From the mucosa, the virus is systemically spread and produces a profound depletion of $CD4^+$ T cells, with monocytes and macrophages also acting as cellular reservoirs for HIV-1 [3]. The viral entry through the mucosa of the gastrointestinal tract can be mediated by the binding of the DC-SIGN receptor, expressed on DCs, to the viral gp120 protein [2]. This interaction appears to be more pronounced in the tonsils at the top of the esophagus and intestinal tract [4].

The infectivity of viruses associated with cells and captured by DC-SIGN is stable even in presence of the acidification process occurring in the gastrointestinal tract, suggesting that the virus bound to DCs through DC-SIGN is protected from the action of the gastric juice. The fact that the free viral particles loose their infectivity when exposed to acidic environments, suggest that the transmission of the virus to free cells in milk is hampered by gastric juice [60]. However, it is possible that free cells become infected in the oral mucosa and esophagus, where the acidity is not high. Studies with Raji cells expressing DC-SIGN, preincubated with PBS and with the HIV-1 virus, showed an efficient viral transfer. However, Raji cells expressing DC-SIGN, incubated with HIV-1 virus and uninfected human milk, showed a significant reduction of the binding of HIV-1 gp120 to DC-SIGN receptor. This suggests that in human milk some factors that could prevent the interaction between the gp120 and DC-SIGN receptor exist [4].

Similar tests were conducted for L-SIGN receptor, however, breast milk did not inhibit the interaction between the viral proteins and the receptor, suggesting that L-SIGN receptor can be used by the virus to increase its infectivity [4]. Some studies also report that exclusive feeding with uninfected mothers' milk during the first months of life protects against a variety of infections, including HIV-1, and help fight morbidity and mortality, suggesting that there should be certain components in the human milk that may protect against the transmission of the virus [59]. So, what are these likely factors in breast milk, and how do they act in protection against the infection caused by HIV-1?

Breast milk is provided with a series of antimicrobial compounds, such as lactoferrin, lysozyme, secretory leukocyte protease inhibitor, lactodifucotetrase, lacto-N-fucopentose I, II, and III, and monofucosilacto-N-hexose III, among others, which are associated with a reduced rate of HIV-1 transmission [2,59]. Some studies attribute this reduction in viral transmission to certain antigens, such as Lewis structures, which compete with the gp120 for a binding site in the DC-SIGN receptor, inhibiting the viral transfer to $CD4^+$ T cells [2]. Inhibition of the binding between gp120 and DC-SIGN receptor is probably due to the size of the compound, which contains many Lewis structures that mask the interaction sites [4]. Compounds containing Lewis structures and present in breast milk were shown to interact with DC-SIGN, blocking the response of Th1 cells and resulting in an increased responsiveness of Th2 cells, suggesting that these compounds may influence the immune response by acting as immunomodulatory factors [4]. A constituent of human milk, bile salt-stimulated lipase, a Lewis X (Le^x)– containing glycoprotein secreted by the pancreas as well as by mammary gland, has been shown to inhibit DC-SIGN binding to HIV and DC-SIGN-mediated transfer of HIV-1 to $CD4^+$ lymphocytes, by competing with the virus for the binding to DC-SIGN [62]. The binding of bile salt-stimulated lipase to DC-SIGN can be prevented using an antibody against Le^x, thus demonstrating the importance of the Le [10] epitope.

Others constituents of human milk, such as human milk oligosaccharides and MUC1 (epithelial mucin), have shown promising results and could be used to develop drugs that inhibit the HIV-1 binding to DC-SIGN [2,59]. Hong et al. [2] found a reduction of more than 60% in the interaction between gp120 and the receptor protein DC-SIGN when using human milk oligosaccharides at a concentration of 0.5 g/l, the one usually present in breast milk. Additionally,

Saeland et al. [59] also described the blocking of the interaction between the gp120 and DC-SIGN receptor in the presence of MUC1 factor, present in human milk. Because of the blockade, there was the prevention of the virus transmission to CD4$^+$ T cells.

Blocking DC-SIGN may be a double-edged sword. It may reduce the entrance of certain viruses, such as HIV-1, but at the same time it may also reduce the ability of the infant's immune system to detect and fight other pathogens [2].

5. Polymorphisms in DC-SIGN and L-SIGN genes and vertical transmission of HIV-1

For some genes, susceptibility and/or resistance to certain (infectious but not only) diseases has been associated with gene expression levels and with the presence of gene variations/mutations. Can this happen also for DC-SIGN and L-SIGN? Can variations in the gene encoding DC-SIGN and L-SIGN be associated with vertical transmission of HIV-1?

To date, except one study regarding the L-SIGN gene, no other genetic studies trying to associate mutations in the genes encoding for DC-SIGN and L-SIGN with the vertical transmission of the HIV-1 have been performed. Boily-Larouche et al. [5] performed an association study in a well-characterized cohort of 197 HIV-1–infected mothers and their children from Zimbabwe, and found that children with two copies of H1 and/or H3 haplotype of L-SIGN were about 3.6 times more at risk for intrauterine transmission of HIV-1 and 5.7 times at risk for intrapartum transmission. The H1 and H3 haplotypes are characterized by two single nucleotide polymorphisms in the promoter region (p-198A) and the intron 2 (int2-180A) that associate with a reduction of the transcriptional activity. The same study also showed that infants homozygous for the H1 haplotype showed a more than fourfold decrease in the level of placental L-SIGN transcripts, and in particular of the membrane linked isoforms [5].

A reduced expression of L-SIGN (especially of the membrane isoforms) in the endothelial cells of capillaries in the placenta may facilitate the binding of HIV-1 to viral entry receptors of endothelial cells, such as CCR5, which can facilitate the migration of maternal HIV-1 across the placental barrier, resulting in intrauterine transmission of HIV-1 [5]. The membrane bound L-SIGN receptors are responsible for catching the virus. After capture, the virus adhered to L-SIGN may undergo degradation processes or be presented as antigens. Thus, these receptors act to protect the infant against infection by HIV-1 [5]. Boily-Larouche et al. [5] explain these discoveries with the hypothesis that when the levels of placental L-SIGN-bound membrane are reduced, virus fails to bind to L-SIGN and binds preferentially to CCR5 receptors on endothelial cells of capillaries, resulting in loss of integrity of the placental barrier and increase the passage of cells infected by HIV-1 in fetal circulation, leading to vertical transmission.

6. Concluding remarks and future directions

In view of what has been discussed, much evidence exist that the DC-SIGN and L-SIGN receptors are involved in the transmission of HIV-1 from mother to child. Therefore, the DC-SIGN and L-SIGN receptors should be likely targets for the development of new drugs and antiretroviral therapies, to challenge the spread of viral transmission.

In addition to this, given that only a few genetic studies have been performed to investigate the possible involvement of DC-SIGN and L-SIGN receptors in the genetic mechanisms correlated with vertical transmission of the HIV-1 virus, we believe that more detailed studies aiming to elucidate the role of genetic variants from different worldwide populations in susceptibility and/or resistance to HIV-1 infection are needed.

References

[1] UNAIDS. Report on the global AIDS epidemic 2008. Geneva, UNAIDS.
[2] Hong P, Ninonuevo MR, Lee B, Lebrilla C, Bode L. Human milk oligosaccharides reduce HIV-gp120 binding to dendritic cell-specific ICAM3-grabbing non-integrin DCSIGNS). Br J Nutr 2009;101:482–486.
[3] Smith PD, Meng G, Salazar-Gonzalez JF, Shaw GM. Macrophage HIV infection and the gastrointestinal tract reservoir. J Leukoc Biol 2003;74:642–9.
[4] Naarding MA, Ludwig IS, Groot F, Berkhout B, Geijtenbeek TBH, Pollakis G, et al. Component in human milk binds DC-SIGN and inhibits HIV transfer to CD4$^+$ T lymphocytes. J Clin Invest 2005;115:3256–64.
[5] Boily-Larouche G, Iscache A-L, Zijenah LS, Humphrey JH, Mouland AJ, Ward BJ, Roger M. Functional genetic variants in DC-SIGNR are associated with mother-to-child transmission of HIV. PLoS ONE 2009;4:e7211.
[6] Luzuriaga K. Mother-to-child transmission of HIV: A global perspective. Curr Infect Dis Rep 2007;9:511–7.
[7] Kimbrell DA, Beutler B. The evolution and genetics of innate immunity. Nat Rev Genet 2001;2:256.
[8] Ben-Ali M, Barreiro LB, Chabbou A, Haltiti R, Braham E, Neyrolles O, et al. Promoter and neck region length variation of DC-SIGN is not associated with susceptibility to tuberculosis in Tunisian patientes. Hum Immunol 2007;68:908–12.
[9] Baribaud F, Pöhlmann S, Doms RW. The role of DC-SIGN and DC-SIGNR in HIV and SIV attachment, infection, and transmission. Virology 2001;286:1–6.
[10] Geijtenbeek TBH, Engering A, Kooyk Y. DC-SIGN, a c-type lectin on dendritic cells that unveils many aspects of dendritic cell biology. J Leukoc Biol 2002;71:921–31.
[11] Steinman RM. DC-SIGN: A guide to some mysteries of dendritic cells. Cell 2000;100:491–4.
[12] Chaudhary O, Rajsekar K, Ahmed I, Verma R, Bala M, Brasin R, Luthra K. Polymorphic varieants in DC-SIGN, DC-SIGNR and SDF-1 in high risk seronegative and HIV patients in Northern Asian Indians. J Clin Virol 2008;43:196–201.
[13] Figdor CG. Molecular characterization of dendritic cells operating at the interface of innate of acquired immunity. Pathol Biol 2003;51:61–3.
[14] Boily-Larouche G, Zijenah LS, Mbizvo M, Ward BJ, Roger M. DC-SIGN and DC-SIGNR genetic diversity among different ethnic populations: Potential implications for pathogen recognition and disease susceptibility. Hum Immunol 2007;68:523–30.
[15] Kooyk YV. C-type lectins on dendritic cells: Key modulators for the induction of immune responses. Biochem Soc Trans 2008;36:1478–81.
[16] Soilleux EJ. DC-SIGN (dendritic cell-specific ICAM-3 grabbing non-integrin) and DC-SIGN-related DCSIGNR): Friend or foe?. Clinical Science 2003;104:437–446.
[17] Khoo U-S, Chan KY, K, Chan VSF, Lin CLS. DC-SIGN and L-SIGN: The signs for infection. J Mol Med 2008;86:861–74.
[18] Alvarez CP, Lasala F, Carrillo J, Muniz O, Corbi AL, Delgado R. C-type lectins DC-SIGN and L-SIGN mediate cellular entry by Ebola virus in cis and in trans. J Virol 2002;76:6841–4.
[19] Cormier EG, Durso RJ, Tsamis F, Boussemart L, Manix C, Olson WC, et al. (CD209L) and DCSIGN(CD209) mediate transinfection of liver cells by hepatitis C virus. Proc Natl Acad Sci U S A 2004;101:14067–72.
[20] Pohlmann S, Zhang J, Baribaud F, Chen Z, Leslie GJ, Lin G, et al. Hepatitis C virus glycoproteins interact with DC-SIGN and DCSIGNR. J Virol 2003;77:4070–80.
[21] Tassaneetrithep B, Burgess TH, Granelli-Piperno A, Trumpfheller C, Finke J, Sun W, et al. (CD209) mediates dengue virus infection of human dendritic cells. J Exp Med 2003;197:823–9.
[22] Halary F, Amara A, Lortat-Jacob H, Messerle M, Delaunay T, Houles C, et al. Human cytomegalovirus binding to DC-SIGN is required for dendritic cell infection and target cell trans-infection. Immunity 2002;17:653–64.
[23] Marzi A, Gramberg T, Simmons G, Moller P, Rennekamp AJ, Krumbiegel M, et al. DC-SIGN and DC-SIGNR interact with the glycoprotein of Marburg virus and the S protein of severe acute respiratory syndrome coronavirus. J Virol 2004;78:12090–5.
[24] Yang ZY, Huang Y, Ganesh L, Leung K, Kong WP, Schwartz O, et al. PH-dependent entry of severe acute respiratory syndrome coronavirus is mediated by the spike glycoprotein and enhanced by dendritic cell transfer through DC-SIGN. J Virol 2004;78:5642–50.
[25] Tailleux L, Schwartz O, Herrmann JL, Pivert E, Jackson M, Amara A, et al. DC-SIGN is the major Mycobacterium tuberculosis receptor on human dendritic cells. J Exp Med 2003;197:121–7.
[26] Bergman MP, Engering A, Smits HH, van Vliet SJ, van Bodegraven AA, Wirth HP, et al. Helicobacter pylori modulates the T helper cell 1/T helper cell 2 balance through phase-variable interaction between lipopolysaccharide and DCSIGN. J Exp Med 2004;200:979–90.

[27] Caparros E, Serrano D, Puig-Kroger A, Riol L, Lasala F, Martinez I, et al. Role of the C-type lectins DC-SIGN and L-SIGN in Leishmania interaction with host phagocytes. Immunobiology 2005;210:185–93.

[28] Lozach PY, Lortat-Jacob H, de Lacroix, de LA, Staropoli I, Foung S, et al. DC-SIGN and L-SIGN are high affinity binding receptors for hepatitis C virus glycoprotein. J Biol Chem 2003;E2:278:20358–66.

[29] Jeffers SA, Tusell SM, Gillim-Ross L, Hemmila EM, Achenbach JE, Babcock GJ, et al. CD209L LSIGNS) is a receptor for severeacute respiratory syndrome coronavirus. Proc Natl Acad Sci USA 2004;101:15748–15753.

[30] Koppel EA, Ludwig IS, Hernandez MS, Lowary TL, Gadikota RR, Tuzikov AB, et al. Identification of the mycobacterial carbohydratestructure that binds the C-type lectins DC-SIGN, L-SIGN and SIGNR1. Immunobiology 2004;209:117–27.

[31] Feinberg H, Mitchell DA, Drickamer K, Weis WI. Structural basis for selective recognition of oligosaccharides by DC-SIGN and DC-SIGNR. Science 2001;294:2163–6.

[32] Geijtenbeek TB, Kwon DS, Torensma R, van Vliet SJ, van Duijnhoven GC, Middel J, et al. DC-SIGN, a dendritic cell-specific HIV-binding protein that enhances trans-infection of T cells. Cell 2000;100:587–97.

[33] Geijtenbeek TBH, Torensma R, van Vliet SJ, van Duijnhoven GCF, Adema GJ, van Kooyk I, Figdor CG. Identification of DC-SIGN, a novel dendritic cell-specific ICAM-3 receptor that supports primary immune responses. Cell 2000;100:575–85.

[34] Pöhlmann S, Soilleux EJ, Baribaud F, Leslie Gj, Morris LS, Trowsdale J, et al. DC-SIGNR, a DC-SIGN homologue expressed in endothelial cells, binds to human and simian immunodeficiency viruses and activates infection in trans. Proc Natl Acad Sci USA 2001;98:2670–5.

[35] Bashirova AA, Geijtenbeek TB, van Duijnhoven GC, van Vliet SJ, Eilering JB, Martin MP, et al. A dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin DCSIGNS)-related protein is highly expressed on human liver sinusoidal endothelial cells and promotes HIV infection. J Exp Med 2001;193:671–678.

[36] Wu L, KewalRamani VN. Dendritic-cell interactions with HIV: Infection and viral dissemination. Nat Rev Immunol 2006;6:859–68.

[37] Granberg T, Zhu T, Chaipan C, Marzi A, Liu H, Wegele A, et al. Impact of polymorphisms in the DC-SIGNR neck domain on the interaction with pathogens. Virology 2006;347:354–63.

[38] Feinberg H, Guo Y, Mitchell DA, Drickamer K, Weis WI. Extended neck regions stabilize tetramers of the receptors DC-SIGN and DC-SIGNR. J Biol Chem 2005;280:1327–35.

[39] Snyder GA, Ford J, Torabi-Parizi P, Arthors JA, Schuck A, Colonna M, Sun PD. Characterization of DC-SIGN/R interaction with human immunodeficiency virus type 1 gp120 and ICAM molecules favors the receptor's role as an antigen-capturing rather than an adhesion receptor. J Virol 2005;79:4589–98.

[40] Zhu D, Kawana-Tachikawa A, Iwamoto A, Kitamura Y. Influence of polymorphism in dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin-related. DCSIGNR) gene on HIV trans-infection. Biochem Biophys Res Commun 2010;393:598–602.

[41] Liu H, Hladik F, Andrus T, Sakchalathorn P, Lentz GM, Fialkow MF, et al. Most DC-SIGNR transcripts at mucosal HIV transmission sites are alternatively spliced isoforms. Eur J Hum Genet 2005;13:707–15.

[42] Martin MP, Lederman MM, Hutcheson HB, Goedert JJ, Nelson GW, Kooyk Y, et al. Association of DC-SIGN promoter polymorphism with increased risk for parenteral, but not mucosal, acquisition of human immunodeficiency virus type 1 infection. J Virol 2004;78:14053–6.

[43] Geijtenbeek TBH, van Vliet SJ, van Duijnhoven GCF, Figdor CG, van Kooyk Y. DC-SIGN, a dentritic cell-specific HIV receptor present in placenta that infects T cells in trans—a review. Placenta;22(Suppl A). Trophoblast Res:15:S19–23.

[44] Sewell AK, Price DA. Dendritic cells and transmission of HIV. Trends Immunol 2001;22:173–5.

[45] Gummuluru S, Rogel M, Stamatatos L, Emerman M. Binding of human immunodeficiency vírus type 1 to immature dendritic cells can occur independently of DC-SIGN and mannose binding C-type lectin receptors via a cholesterol-dependent pathway. J Virol 2003;77:12865–74.

[46] Rappocciolo G, Piazza P, Fuller CL, Reinhart TA, Watkins SC, Rowe DT, et al. DC-SIGN on B lymphocytes is required for transmission of HIV to T lymphocytes. PLoS Pathog 2006;2:e70.

[47] Wichukchinda N, Kitamura Y, Rojanawiwat A, Nakayama EE, Song H, Pathipvanich P, et al. The polymorphisms in DC-SIGNR affect susceptibility to HIV type 1 infection. AIDS Res Hum Retrovir 2007;23:686–92.

[48] Borggren M, Repits J, Kuylenstierna C, Sterjovski J, Churchill MJ, Purcell DFJ, et al. Evolution of DC-SIGN use revealed by fitness studies of R5 HIV variants emerging during AIDS progression. Retrovirology 2008;5:28.

[49] Hirbod T, Kaldensjö T, Lapalco L, Klareskog E, Andersson S, Uberti-Foppa C, et al. Abundant and superficial expression of c-type lectin receptors in ecto-cervix of women at risk of HIV infection. J Acquir Immune Defic Syndr 2009;51:239–47.

[50] Selvaraj P, Alagarasu K, Swaminathan S, Harishankar M, Narendran G. CD209 gene polymorphisms in South Indian HIV and HIV-TB patients. Infect Genet Evol 2009;9:256–62.

[51] Lee B, Leslie G, Soilleux E, O'Doherty U, Baik S, Levroney E, et al. Cis expression of DC-SIGN allows for more efficient entry of human and simian immunodeficiency viruses via CD4 and a co-receptor. J Virol 2001;75:12028–38.

[52] Mummidi S, Catano G, Lam L, Hoefle A, Telles V, Begum K, et al. Extensive repertoire of membrane-bound and soluble dendritic cell-specific ICAM-3-grabbing nonintegrin 1. DCSIGNS;1 and DC-SIGN2 isoforms. J Biol Chem 2001;276:33196–212.

[53] Velilla PA, Montoya CJ, Hoyos A, Moreno ME, Chougnet C, Rugeles MT. Effect of intrauterine HIV exposure on the frequency and function of uninfected newborns' dendritic cells. Clin Immunol 2008;126:243–50.

[54] Soilleux EJ, Morris LS, Lee B, Pöhlmann S, Trowsadale J, Doms RW, Colleman N. Placental expression of DC-SIGN may mediate intrauterine vertical transmission of HIV. J Pathol 2001;195:586–92.

[55] Soilleux EJ, Coleman N. Transplacental transmission of HIV: A potential role for HIV binding lectins. Int J Biochem Cell Biol 2003;35:283–7.

[56] Newell ML. Mechanisms and timing of mother-to-child transmission of HIV. AIDS 2006;12:831–7.

[57] Moussa M, Mognetti B, Dubanchet S, Menu E, Roques P, Gras G, et al. Vertical transmission of HIV: Parameters which might affect infection on the study of in utero transmission of HIV 1. Am J Reprod Immunol 1999;41:312–9.

[58] Shen R, Smythies LE, Clements RH, Novak L, Smith PD. Dendritic cells transmit HIV through human small intestinal mucosa. J Leukoc Biol 2010;87:1–8.

[59] Saeland E, Jong MAWP, Nabatov AA, Kalay H, Geijtenbeek TBH, Kooyk YV. MUC1 in human milk blocks transmission of human immunodeficiency virus from dendritic cells to T cells. Mol Immunol 2009;46:2309–16.

[60] Satomi M, Shimizu M, Shinye E, Watari E, Owaki A, Hidaka C, et al. Transmission of macrophage-tropic HIV by breast-milk macrophages via DC-SIGN. J Infect Dis 2005;191:174–81.

[61] Ichikawa M, Sugita M, Takahashi M, Satomi M, Takeshita T, Araki T, et al. Breast milk macrophages spontaneously produce granulocyte-macrophages colony-stimulating factor and differentiate into dendritic cells in the presence of exogenous interleukin-4 alone. Immunology 2003;108:189–95.

[62] Naarding MA, Dirac AM, Ludwig IS, Speijer D, Lindquist S, Vestman EL, et al. Bile salt-stimulated lipase from human milk binds DC-SIGN and inhibits human immunodeficiency virus type 1 transfer to CD4$^+$ T cells. Antimicrob Agents Chemother 2006;50:3367–74.