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Review

The role of semen in sexual transmission of HIV: beyond a carrier for virus particles

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Abstract

Unprotected sexual intercourse between discordant couples is by far the most frequent mode of HIV-1 (human immunodeficiency virus type 1) transmission being semen the main vector for HIV-1 dissemination worldwide. Semen is usually considered merely as a vehicle for HIV-1 transmission. In this review we discuss recent observations suggesting that beyond being a carrier for virus particles semen markedly influences the early events involved in sexual transmission of HIV through the mucosal barriers.

Keywords: Semen; Spermatozoa; HIV-1; Inflammation; Dendritic cells

1. Introduction

Since the beginning of the AIDS epidemic more than 35 million adults and children worldwide have died from AIDS. The number of people living with HIV is growing due to the beneficial impact of antiretroviral therapy and the continued high rates of new HIV infections. The UNAIDS/WHO AIDS epidemic uptade has recently estimated that 33 million people were living with HIV at the end of 2009. Moreover, during 2009 an estimated 2.7 million new HIV infections occurred worldwide and almost 2 million individuals succumbed due to AIDS-related illnesses [1].

Unprotected sexual intercourse between discordant couples is the major route of HIV-1 infection with semen being the major transmission vector [2,3]. Semen contains three major sources of infectious virus: free virions, spermatozoa-associated virions, and infected leukocytes [2–7]. Their participation in sexual transmissions of HIV-1, however, is not well defined. Free virus and seminal infected leukocytes appear to play an important role [2–4,6,7]. By contrast, the role of spermatozoa has been a matter of debate [8–12] in spite that the presence of HIV-1 particles and nucleic acids in the spermatozoa has been largely shown using a variety of techniques [13–18].

After deposition of HIV-1 on the recipient mucosa, infectious virus must cross the mucosal epithelium to interact with the three major targets of HIV-1 infection, CD4+ T lymphocytes, macrophages and dendritic cells (DCs). These cells express the receptor CD4 and the coreceptors CXCR4 or CCR5 which are required for HIV-1 infection [2,4–7]. The mechanisms through which HIV-1 traverses the mucosal barriers and establishes infection are not well defined. The virions might transcytose through the genital epithelium [4,6] or might pass through genital lesions [19–21]. Epithelial microabrasions in the vagina are detected in 60% of healthy women after consensual intercourse [22,23], suggesting that they constitute a frequent scenario for the sexual transmission of HIV-1. Although HIV-1 can infect target cells in the vaginal, ectocervical and endocervical mucosa, the contribution of each of these sites to the establishment of the initial

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infection is not defined. Anal intercourse is also often associated to mucosal trauma and, because the rectal epithelium is only one cell layer thick, it provides a low degree of protection against trauma, favouring the access of virus to the underlying target cells [3]. Of note, single-genome amplification and sequencing of the earliest detectable viruses showed that they are usually derived from a single transmitted virus which infects a small founder population of CD4+ T cells [5,24,25]. HIV-1 remains localized in the genital mucosa for about a week defining the "eclipse phase" of the infection [5,26], which provides a window opportunity for intervening in order to prevent the establishment of the infection. Then, the infection spreads to gut-associated lymphoid tissues (GALT) where high levels of virus replication take place leading to a dramatic increase in plasma viral titres [5,26].

Interestingly, epidemiological studies show that HIV-1 is not particularly easy to be acquired by sexual contact. The incidence of sexual transmission of HIV-1 is relatively low and appears to vary by anatomical site. Anal sex has the highest risk (1:20 to 1:300 for each sexual act), while vaginal sex has a lower risk (1:1000 to 1:10,000) [27–29]. As expected, the risk of infection is strongly dependent on the phase of the infection and is almost 10-fold higher during acute infection [30]. Other factors, such as coexisting sexually transmitted infections (STIs) strongly increase the risk of infection [27–30]. For example, it has been reported that HSV-2 infection induces a threefold increase in susceptibility to HIV-1 infection [31]. This appears to be related to the induction of ulcerations by HSV-2, which creates a breach in the genital epithelium barrier as well as to the local recruitment and persistence of CD4+ target cells in the exposed mucosa [31,32].

When thinking about HIV-1 transmission *in vivo* it should be emphasized that semen is the most frequent vehicle for HIV-1 spread. Semen contains a diverse array of components, including carbohydrates, lipids, peptides, proteins, cytokines, and chemokines, produced from different sources: the testis, epididymis, and accessory glands [33,34]. The concentration of proteins in the seminal plasma ranges from 35 to 55 g/L, and proteomic analysis led to the identification of more than 900 proteins [35,36]. We think that semen might play an important role in HIV-1 transmission beyond its role as a carrier for delivery of HIV-1 during receptive vaginal or anal intercourse. Supporting this view many studies have provided insights into the effects mediated by semen components on both, the virus and the mucosal HIV-1 entry sites. In this review, we will highlight both what is known and unknown about the different mechanisms through which semen might favour or interfere with HIV-1 transmission.

2. Enhancement of HIV-1 infection by semen

2.1. Spermatozoa efficiently transmit HIV-1 to dendritic cells

Dendritic cells (DCs) are highly specialized antigen-presenting cells with a unique ability to activate resting T lymphocytes and to initiate primary immune responses. Upon encountering PAMPs (pathogen-associated molecular patterns), DAMPs (damage-associated molecular patterns) or inflammatory cytokines in peripheral tissues, DCs become activated and undergo a set of changes leading to both, the migration to lymph nodes and their phenotypic maturation [37,38].

Owing to their localization at mucosal surfaces, the expression of CD4, CCR5 and CXCR4, the expression of a number of additional cell surface molecules able to attach HIV-1, and their high endocytic ability, DCs appear to be an early and important target of HIV-1 during sexual transmission [39,40]. Although DCs are relatively resistant to infection with HIV-1, some populations of DCs are able to capture HIV-1 at entry sites and transport the virus to draining lymph nodes, where HIV-1 is efficiently transmitted to T CD4+ cells, which become the centre of viral replication. This mechanism appears to play an important role in the spreading of HIV-1 infection [39–41].

We have recently reported that spermatozoa greatly enhance the infection of DCs by HIV-1 [42]. Our observations revealed that spermatozoa efficiently attach and transmit the virus to DCs. In fact, the ability of spermatozoa-attached viruses to infect DCs appears to be substantially greater compared with free viruses (Ceballos A, unpublished data). Interestingly, spermatozoa-attached HIV are also efficiently transmitted to macrophages and CD4+ T cells, suggesting that HIV-1 might exploit its ability to attach to the surface of the spermatozoa in order to improve infectivity. Of note, we found that acidic values of extracellular pH, similar to those found in the vaginal mucosa after sexual intercourse (i.e., pH 6.5) [43,44], markedly increase the binding of HIV-1 to the spermatozoa surface and the consequent transmission of HIV-1 to CD4+ target cells [42]. We hypothesize that spermatozoa might favour the sexual transmission of HIV-1 by promoting the infection of dendritic cells, macrophages and CD4+ T cells. Further studies in animal models are needed to test this hypothesis.

2.2. Semen raises the pH of vaginal secretions improving the infectivity of HIV-1

The healthy vaginal environment is acidic (pH 4.0–6.0) [45], by contrast, the pH of the normal semen is slightly alkaline ranging from 7.2 to 7.8 [46]. Because laboratory strains of HIV-1 are usually inactivated after exposure to pH values lower than 5 [47], it is generally assumed that the acidic environment of the vagina provides a protective mechanism against sexual transmission of HIV-1 [3,7]. Semen might counteract this protective mechanism. In fact, deposition of semen in the vagina increases the pH of the vaginal mucosa to values of 6.0–7.0 for several hours after sexual contact [43,44].

Recent studies done with primary isolates instead of laboratory strains showed a high variability of HIV-1 to inactivation by acidic pH. In fact, for certain isolates it was reported that the infectivity of HIV-1 was actually enhanced after exposure to pH 4.0–5.0 [48]. Taking this into account, and

also considering that acidic values of pH induce a number of biological responses that might favour the transmission of HIV-1 such as an increased association of HIV-1 to the spermatozoa [42], the activation and maturation of DCs [49], and the activation of the complement system [50–52], we think that the overall influence of vaginal pH on HIV-1 transmission should be rigorously re-examined.

2.3. Semen induces an inflammatory reaction in the female reproductive tract

Semen deposition in the mucosa of the female reproductive tract results in the induction of a strong inflammatory response. Using ectocervical epithelial cells, Sharkey and coworkers [53] showed that seminal plasma induces the production of a number of inflammatory cytokines and chemokines such as IL-8, MCP-1, IL-6, and GM-CSF. Consistent with this observation, serial analysis of cervical smearing revealed that semen deposition induces the infiltration of the cervix by neutrophils and, to a lesser extent, by macrophages and T lymphocytes [54,55]. Moreover, Berlier and coworkers showed that seminal plasma promotes the attraction of Langerhan cells via the stimulation of CCL20 secretion by vaginal epithelial cells [56]. Seminal plasma also induces the expression of cyclooxygenase-2, the rate-limiting enzyme for prostanoid synthesis, in human vaginal cells [57]. What is the meaning, if any, of the inflammatory response induced by semen in the female reproductive mucosa? We do not yet know the answer to this question. Interestingly, it is becoming increasingly clear that different normal reproductive processes such as ovulation, menstruation, implantation and parturition display hallmark signs of inflammation [58–61]. Whether or not the inflammatory responses induced by semen deposition in the mucosa affect the course of the early events involved in the fertilization or the implantation processes remains to be determined. Similarly, these inflammatory responses may contribute to the transmission of HIV-1 and other sexually transmitted infectious diseases through two major mechanisms: a) by disrupting the epithelial barrier, and b) by inducing the local recruitment of CD4+ target cells favouring the dissemination of HIV-1 infection [54–56].

2.4. Semen-derived amyloid fibrils enhance HIV-1 infection

A novel mechanism through which semen might favour sexual transmission of HIV-1 has been proposed by Munch and coworkers [62].The authors screened a complex peptide/protein library derived from human seminal plasma for novel inhibitors and enhancers of HIV-1 infection. They found that naturally occurring fragments of the abundant semen protein prostatic acidic phosphatase form amyloid fibrils termed semen-derived enhancer of virus infection (SEVI) which markedly increased HIV-1 infection.

Functional and structural studies showed that SEVI capture HIV particles enhancing the number of infected cells by promoting the attachment of the virus to the cell surface. SEVI appears to act as a general enhancer of HIV-1 infection. It increases the infection by R5-, X4- and dual tropic HIV-1 clones in peripheral blood mononuclear cells (PBMCs), macrophages and DCs. Further studies revealed that the promotion of HIV-1 infection mediated by SEVI is strongly dependent on its cationic nature (isoelectric point = 10.21). This property enables SEVI to non-specifically interact with HIV favouring the attachment and fusion of the virus to the target cell surface promoting HIV infection [63]. The enhancing effect mediated by SEVI was also tested *in vivo* using hCD4/hCCR5-transgenic rats challenged with HIV-1 or SEVI-treated HIV-1 by tail vein injection. Pre-treatment of HIV with SEVI resulted in a 5-fold increase in the number of copies of HIV-1 cDNA found in the splenocyte extracts from infected rats [62].

The great increase in the infectivity of HIV-1 when the virus is treated in vitro with SEVI, suggests that it might favour sexual transmission of HIV-1. However, the reproducibility of the enhancing effect has shown a high variability depending of the individual semen donor [64]. In addition, and in direct contrast with these results, two recent studies have shown that seminal plasma does not enhance, but rather it significantly suppresses the infection of CD4+ T cells by HIV-1 [65,66], raising some concerns about the relevance of SEVI in sexual transmission of HIV. Further testing of the ability of SEVI to enhance HIV infection in animal models is required to define its role in sexual transmission of HIV.

2.5. Semen contains high concentrations of immunomodulatory agents able to suppress the innate and adaptive immune response against HIV

It is well known that semen is able to suppress a number of immune responses mediated by both the innate and adaptive immune system [67,68]. These immunosuppressive actions appear to play an important role in human reproduction. They enable spermatozoa to survive in the female reproductive tract, to induce a state of non-responsiveness to sperm antigens, to promote a tolerogenic response to paternal alloantigens favoring maternal acceptance of the conceptus at implantation, and to avoid allogeneic fetal rejection [67–73].

The mechanisms underlying the suppression of the immune response mediated by semen are not clearly defined but they appear to be related, at least in part, to the presence of extremely high concentrations of TGF-β and PgE2 in the semen. It contains more active TGF-β (∼ 1 ng/ml) than do other body fluids. Moreover, semen contains a huge amount of inactive or latent TGF-β (∼ 80 ng/ml) which can be activated by either the acidic vaginal pH or enzymes found in vaginal secretions or seminal plasma [67,68,72,73]. The concentration of PgE2 in human seminal plasma is also extremely high reaching levels of 100 μg/ml (74). Immunosuppression mediated by TGF-β and PgE2 involves a number of mechanisms acting on different immune cells. They inhibit the activation of neutrophils, natural killer cells, and macrophages. Moreover, both compounds induce the differentiation of DCs into a regulatory profile and promote the development of T regulatory responses [74–76].

Surprisingly, the impact of semen TGF-β and PgE2 on the ability of the receptive partner to induce an immune response against sexually transmitted infectious diseases has not been defined yet. However, it is reasonable to speculate that the immunosuppressive effects mediated by both compounds are not restricted to spermatozoa antigens and paternal alloantigens and also influence the course of the immune response against HIV and other sexually transmitted agents favoring the spreading of the infectious processes [71].

3. Inhibition of HIV infection by semen

3.1. Semen inhibits the attachment of HIV-1 to DC-SIGN-expressing dendritic cells

Langerin-expressing epithelial Langerhans cells and DC-SIGN-expressing subepitehlial cells are the two major DC populations found in the female reproductive tract [77]. Interestingly, they appear to mediate opposite effects on the initial spreading of HIV-1 infection due, at least in part, to differences in the intrinsic functions of langerin and DC-SIGN, two members of the C-type lectin family of pattern recognition receptors (PRR). The capture of HIV-1 by Langerhans cells through langerin leads to the internalization and degradation of viral particles, which protects Langerhans cells from infection, preventing the spreading of HIV-1 [78,79]. By contrast, the binding of HIV-1 to DC-SIGN promote the dissemination of infection. HIV-1 seems to exploit DC-SIGN binding to promote both, the infection of DCs and the transmission of HIV-1 to CD4+ T cells [80,81].

Importantly, DC-SIGN-expressing DCs are found not only in the female reproductive tract, but also in the rectal mucosa. Supporting a role for DC-SIGN in the transmission of HIV-1 through the rectal mucosa, studies performed in HIV-infected patients showed that almost 90% of the virus associated to the mononuclear cells from the rectal mucosa is bound to DC-SIGN-expressing DCs, which only represents a minor fraction (1–5%) of the population of mononuclear cells found in the rectal mucosa [82]. Of note, recent studies suggest that the role of DC-SIGN in promoting the spreading of HIV-1 is not only related to the ability of DC-SIGN to recognize and attach the virus to the DC surface. Binding to DC-SIGN also triggers a signaling pathway mediated by Raf-1 which is required for the generation of full-length viral transcripts and HIV-1 replication in DCs [83]. Together, these observations suggest an important role for DC-SIGN in sexual transmission of HIV-1 and support the notion that targeting of DC-SIGN might be an interesting approach to stop the dissemination of HIV-1 infection at the mucosal entry sites.

In this sense we have shown the impact of seminal plasma in the interaction between HIV-1 and DC-SIGN. We found that human seminal plasma, even when used at very high dilutions ($1:10^4$ to $1:10^5$), abrogates the recognition of HIV-1 by DC-SIGN. Not only the binding of HIV-1 to monocyte-derived DCs (which express high levels of DC-SIGN) but also the transmission of HIV-1 from DCs to T CD4+ cells was markedly inhibited by seminal plasma [84]. The inhibitory effect mediated by seminal plasma appeared to be specific for DC-SIGN since no inhibitory effect was observed using DC-SIGN-negative target cells such as the T-cell line Sup T-1, monocytes and activated CD4+ T cells. Inhibition of DC-SIGN mediated-capture of HIV-1 by seminal plasma was confirmed recently in two independent studies [64,85].

Additional studies in our group identified semen clusterin as the main ligand for DC-SIGN present in the semen (Sabatté J, unpublished results). Semen clusterin accounts, at least in part, for the inhibitory effect of semen on the capture of HIV-1 mediated by DC-SIGN. It efficiently inhibits the attachment to, and the infection of DCs, but not CD4+ T cells, by HIV-1. Our results suggest that the high concentration of clusterin in human semen (0.4–15 mg/ml) might exert a preventive effect on sexual transmission of HIV-1 as well as of other pathogens that misuse DC-SIGN to promote its own infectivity such as *hepatitis C* virus, *herpes simplex* virus, *Neisseria gonorrhoeae*, and the fungi *Candida albicans* [86].

4. Conclusions

The influence of semen in HIV-1 transmission remains controversial. Surprisingly, little attention has been paid to define this point, in spite that semen is the most important vector for HIV-1 transmission. Semen components appear to be able to mediate both, enhancing and inhibitory effects on HIV-1 infection and transmission. Further experiments are needed, especially in animal models, to define the overall influence of semen in sexual transmission of HIV-1.

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