Actas Urológicas Españolas

www.elsevier.es/actasuro

Review – Inflammation-Infection

Virus of Sexual transmission: Semen and virus relationship

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ARTICLE INFORMATION

Article history:
Received 31 March, 2010
Accepted 21 July, 2010

Keywords:
Viruses
Spermatozoa
Sexual transmission infections
Semen

A B S T R A C T

Introduction: The possible "infection"/interaction processes between sperm and different microorganisms are under discussion nowadays. This process might include some viruses and even recent investigations are aiming to elucidate the mechanisms and the receptors that may be involved in this interaction. Furthermore, the presence of some viral genomes within the sperm DNA has been reported, raising the possibility of transmitting the infection to the partner and offspring.
Objective: The aim of this review is to describe the mechanisms of how viruses could possibly infect some seminal fractions. This is pursued by performing a literature review for answering the question: how could the sexually transmitted virus be infecting sperm?
Materials and methods: We carried out a bibliographic review on sperm and virus interaction.
Results: Some viruses interact with sperm cells; and sperm cells could transfer the viruses to offspring, however, in most cases, the receptors that allow this interaction are not clearly described.
Conclusions: Based on the current information, new in vitro studies are needed to determine the role of sperm in spreading viruses of sexually transmitted infections.

Virus de transmisión sexual: relación semen y virus

Palabras clave:
Virus
Espermatozoide
Infecciones de transmisión sexual
Semen

R E S U M E N

Introducción: Actualmente, existe debate sobre la posibilidad de «infección»/interacción de los espermatozoides con diferentes virus, inclusive para algunos virus se intentan dilucidar mecanismos y receptores que podrían estar involucrados en esta interacción. Adicionalmente, se ha reportado la presencia de algunos genomas virales en el DNA espermático, planteando la posibilidad de transmitir la infección a la pareja y a la descendencia.
Objetivo: En la presente revisión se pretende describir los mecanismos de infección de algunos virus a las fracciones seminales, pretendiendo mediante una revisión bibliográfica, responder a la pregunta ¿cómo los virus de transmisión sexual infectan al semen?
Materiales y métodos: Se realizo una búsqueda bibliográfica sobre la interacción de virus y espermatozoides.

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0210-4806/$ - see front matter

Resultados: Algunos virus pueden interactuar con los espermatozoides y estos podrían transferir el virus a la descendencia; sin embargo, en la mayoría de los casos, los receptores que permiten esta interacción no están claramente descritos.
Conclusiones: A pesar de la información actual, nuevos estudios experimentales son necesarios para determinar el papel de los espermatozoides en la diseminación de las infecciones de transmisión sexual.

Introduction

Semen may be infected by several microorganisms such as bacteria, fungi, parasites, and viruses, which find in seminal plasma optimum conditions for survival. Some of these agents cause sexually transmitted diseases (STDs) such as syphilis, gonorrhoea, lymphogranuloma venereum, genital herpes, granuloma inguinale, and papilloma, among others.[1] Among these microorganisms, sexually transmitted viruses play a special role not only because they cause infections and some asymptomatic, difficult to treat unknown diseases which have dramatically increase in recent years,[2] but also because they may be stored, transported, and transmitted by sexual contact to the partner or offspring.[3]

The blood-testis barrier isolates sperm cells from all other body compartments.[4] However, when this barrier is crossed by any virus, this remains active or latent and may subsequently be transported by the male reproductive system (MRS), especially in semen, which contains a heterogeneity of components: i) cell fraction: sperm cells, white blood cells, and epithelial cells; and ii) plasma fraction.[2]

Specifically, the Epstein-Barr virus (EBV) has been found to be present in seminal plasma, and it has been suggested that semen could facilitate dissemination of EBV in both MRS and the female reproductive system (FRS).[2] In addition, healthy women undergoing assisted reproduction procedures have been found to be infected with HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV), which would suggest that spermatozoa are involved in transmission of infection.[5] On the other hand, the presence of some viruses in semen and their potential role in transport by spermatozoa to the oocyte have been reported in bovine[6] and feline[7] models.

The purpose of this review was to describe the mechanisms by which herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), human papilloma virus (HPV), HIV, HBV, HCV, and human cytomegalovirus (HCMV) infect seminal fractions, and to try and answer the question: how do sexually transmitted viruses infect semen? based on a literature review.

Methods

Information collection and management

Information was simultaneously collected for all viruses to be analyzed through a comprehensive search for scientific information in Pubmed (http://www.ncbi.nlm.nih.gov).

Information inclusion and exclusion criteria

a) Information on the following subjects: semen, spermatozoa, male reproductive system, sexually transmitted disease, AIDS, receptors, herpes simplex viruses 1 and 2, human papilloma virus, human immunodeficiency virus, hepatitis B virus, hepatitis C virus, cytomegalovirus, co-infections, and viruses transmitted to the offspring; b) information within a time range (approximately 20 years) for each virus; and c) information in both Spanish and English.

Analysis of information

First reading: Inclusion and exclusion criteria were applied to all information collected in order to filter such information and note any deficiencies and strengths. *Second reading:* Filtered information was read again to classify it by chapter based on viruses. *Data analysis and discussions:* Analysis of data supporting the proposed theories and discussions of equivocal information to allow for drawing a specific conclusion regarding the problem posed. *Manuscript preparation.*

Bias control

Potential bias included: i) information collected from a non reliable source, and ii) poor translation of information into Spanish. To avoid such bias, suggestions by the thematic advisor of the project were followed, as he had more experience on the subject and had a good grasp of technical language.

Viruses

Human immunodeficiency virus

HIV is the most widely studied virus worldwide today, probably because of the number of patients reported to suffer from HIV infection, more than 43 million in 2007.[8] HIV, a member of the *Retroviridae* family and the *lentivirus* genus, is an enveloped virus with two simple RNA chains. HIV has tropism for cells expressing the CD4 molecule in their membranes, such as macrophages, T cells, dendritic cells, among others.[9]

Semen has been suggested to be a fluid carrying HIV,[9] and it has been established that there are different factors promoting MRS infection by HIV, including: a) co-infection with other microorganisms causing STIs which create conditions that increase the infectious potential of virus in semen; b) the blood-testis barrier and locally produced immunosuppressant factors, which may protect the virus from the immune response of the body at certain MRS regions; and c) antiviral drugs not adequately penetrating into certain MRS regions.[10]

It has been reported that spermatozoa may be "infected" with the virus, as a viral genome has been found in the spermatozoa of HIV-positive subjects.[11] This suggested the presence of different HIV interaction and internalization mechanisms in CD4-negative cells due to the absence of CD4 receptors in spermatozoa membrane.[11]

In vasectomized HIV-positive patients, viral concentration would be expected to vary in seminal cells and secretions deposited in the prostate, seminal vesicles, urethra, and Cowper glands because vasectomy prevents passage of molecules and other components from the testes. However, quantitative PCR has shown in some of these patients that levels of both viral RNA and free particles in seminal plasma remain constant as compared to pre-vasectomy levels, and viral particle levels in the cell fraction of semen and seminal white blood cell levels dramatically increased after vasectomy, possibly due to the inflammation of deferent ducts occurring after the surgical procedure.[12]

In vitro tests have shown human spermatozoa to be able to interact with glycoprotein gp120 of the virus, suggesting that virus entry into the spermatozoon is not only due to conventional receptors, but there are other alternative receptors contributing to the process such as Gal-AAG, mannose receptors, DC-SIGN or, more recently, heparan sulphateo.[13,14]

Finally, as regards potential horizontal or vertical virus transmission, and assuming the spermatozoon carries the viral agent, such transmission is hardly conceivable, though not impossible, because after virus binding to the spermatozoon, this has to make a long journey through the female reproductive tract (FRT) to interact with and fertilize the oocyte, and in this process, virus in the "infected" spermatozoa may be shed and even disintegrated by the adverse conditions of the FRT medium such as pH and temperature.[15] There were however three subjects born from serum-discordant couples (HIV-negative mothers and HIV-positive fathers) which allowed for speculating about a potential vertical transmission from father to child[16,17] and even for postulating a model of spermatozoa-HIV interaction both *in vivo* and *in vitro*.[18]

Herpes simplex virus type 1 and 2

The *Herpesviridae* family is divided into three subfamilies, *alpha-*, *beta-, and gammaherpesvirinae*, including the approximately 100 herpesviruses reported to date. HSV-1 has usually been associated to cold sores, and HSV-2 to genital herpes. However, both of them may infect and damage both areas of the body, and the two types of lesions are indistinguishable. The two types of virus have a double-stranded DNA chain compacted within a capsid with icosahedral symmetry and a lipid membrane. Both viruses have tropism for epithelial cells in the skin, mucosal membranes, neurons, and white blood cells.[19]

Specifically, HSV-2 is the most common cause of genitourinary viral infections. In the United States, more than 20 million people have genital herpes, and more than half a million new cases are reported every year.[19] The high prevalence of this virus is due, among other reasons, to its easy transmission from one person to another by skin and mucosal contact, as occurs with very common practices in humans such as kissing and sexual intercourse. The most remarkable characteristic of infection by this virus is that it never disappears from the body, but enters into a latent state in lymph nodes, causing no symptoms. However, certain stimuli, mainly including compromised cell immunity, cause reactivation of the virus and disease recurrence.[19]

HSV-2 may infect most MRS organs, including the prostate,[2] but not seminiferous tubules because of the protection conferred by the blood-testis barrier. However, semen may be infected as it passes during ejaculation. An asymptomatic subject infected by the virus transmitted it by the sexual route to his HSC-2-negative partner, who subsequently developed genital herpes.[2] Electron microscopy did not show binding to human spermatozoa. However, *in situ* hybridization did find an association between sperm cells and viral DNA, particularly in patients with fertility problems.[20] In addition, in a study conducted by Pallier et al., HSV-2 was found in both the plasma and cell fractions.[21]

A close ligand/receptor interaction may exist between the virus and seminal cells, as many herpes virus entry receptors have been reported. Such receptors mainly include:

a) Glycosaminoglycans (GAGs), especially heparan sulphate, located in cell surface, which is able to mediate entry of many viruses, including HSV-1 and HSV-2. In bovine and porcine models, heparin plays a significant role both in the sperm enabling process and for preparation of interaction with the oocyte because spermatozoa have a heparin receptor.[22]
b) Nectin-1 and nectin-2, members of the immunoglobulin superfamily also known as HveC and HveB, are expressed in many organs, tissues, and cell lines, particularly endothelial and epithelial cells, fibroblasts, and neurons, which are commonly infected by HSV. Nectin-1 expression on murine spermatids, which would promote interaction with the virus, has also been seen.[19]
c) A mannose receptor, a lectin-like receptor. The gD of HSV has been shown to be able to interact with mannose receptors located on the surface of many cell lines.[23]

Human cytomegalovirus

Human cytomegalovirus (HCMV) is a *betaherpesvirinae* that belongs to the herpesvirus family. Its genome, linear double-

stranded DNA, is the longest of all herpes viruses. HCMV is highly pathogenic and opportunistic. Infection by the virus mainly occurs in immunocompromised subjects and newborns, in whom immune system is "immature" and cannot control infection.

The cell receptor for virus entry has not been clearly elucidated to date, but should be widely distributed among the different cells susceptible to infection, including amongst others epithelial and endothelial cells, hepatocytes, monocytes, macrophages, and neutrophils. HCMV may be excreted for a long time in biological fluids, including semen, and may be transmitted horizontally and vertically.[24] It should be stressed that no significant differences have been found in sperm motility as the result of semen infection by HCMV.[21]

Studies conducted with a virus of another species, MCVM (murine cytomegalovirus), found that when the virus was injected into mouse testes, viral DNA could be isolated using different molecular techniques from both immature sperm cells and mature spermatozoa. The virus also caused inflammatory infiltrates in the reproductive tract, interstitial cell infection, and degeneration of seminiferous tubules. Leydig cells were the preferred target for viral invasion.[25]

The mechanism most widely accepted today is that the virus first adheres to heparan sulphate, but its final entry into the cell is mediated by some of those unknown receptors. The main postulated receptors include:

a) Epidermal growth factor receptor (EGFR), which may have a significant role in viral adhesion and genetic expression. Its role has however been questioned because some cells susceptible to viral infection, such as monocytes, macrophages, and neutrophils, do not express EGFR on their surface.[26]
b) Cell integrins, such as $\alpha_2\beta_1$, $\alpha_6\beta_1$, and $\alpha V\beta_3$, as the N-terminal region of gB of HCMV has been shown to have a highly conserved domain very similar to a fraction of those integrins, which allows them to interact, suggesting a major role of these as co-receptors in cell adhesion and entry.[27] Other studies suggest that integrin $\alpha V\beta_3$ acts as co-receptor with EGFR, binding to gH and gB of the virus respectively.[6]
c) β_2-microglobulin has been postulated to be not only a receptor for HCMV adhesion, but also a molecule that helps enhance virus infectivity by competing for binding to class I HLA and suppressing its expression on the surface of virus-infected cells, which would be a good mechanism for evading immune response.[28]

The HCMV genome found in infected newborns has been shown to be of the same type as found in their parents, which could suggest that the virus may be transmitted from the mother or father to the fetus.

Hepatitis B and C viruses

There are various types of virus causing hepatitis, a disease having the liver as the target organ. Viral agents reported to date to cause hepatitis include hepatitis A, B, C, D, E, and G viruses. HBV and HCV are described below because these two types have been found in semen and are probably transmitted by this route to the sexual partner.

Hepatitis B virus

The hepatitis B virus (HBV), a member of the *Hepadnaviridae* family, has a circular, double-stranded DNA genome of 3.2 Kb. The virus has an envelope and complex symmetry. The virion mainly consists of three envelope proteins called large (L), of 39kDa, middle (M), of 32kDa, and small (S), of 24kDa, which form together the surface antigen (HBsAg).

More than one third of the world population is infected by HBV, which causes one or two million deaths every year. HBV is responsible for acute and chronic hepatitis and hepatocellular carcinoma. It has been found in various body fluids such as blood, saliva, breast milk, vaginal secretions, and semen, and is mainly transmitted by the parenteral, sexual, and perinatal routes.[29] Hepatitis B is also known to be a disseminated disease acquired through the epithelium and mucosal membranes and having hepatocytes as target cells.

Some patients in whom the viral genome has not been found in serum transmit HBV through sexual contact, which suggests that the MRS serves as a reservoir for the virus.[30] Molecular techniques have also found HBV DNA sequences integrated into sperm chromosomes, where the virus has possibly crossed the blood-testis barrier and infected the male germ line. Such infection may cause mutagenic effects on sperm chromosomes, leading to instability and hereditary defects, in addition to potential vertical transmission of HBV to the offspring.[31] Huang et al. assessed, using various molecular techniques such as PCR, Southern blot, and FISH, the possibility that HBV DNA could be integrated into mouse oocytes and detected viral genome sequences in oocyte chromosomes,[31] which supported the possibility that the fetus may acquire infection from the mother.

The mechanism by which HBV infects the target cell is still unknown. The receptor that binds the viral particle and mediates virus entry into the cell by endocytosis has not been identified. However, studies have found that the preS1 domain in envelope protein L of HBV is closely linked to the target cell recognition and binding process; some studies showed that: a) deletion of five amino acids in the sequence between amino acids 3 and 77 of preS1 prevented infection in primary human hepatocytes,[32] and b) antibodies to the N-terminal region of the preS1 domain blocked *in vitro* HBV infection of cultures of primary hepatocytes from *Tupaia belangeri*, a small mammalian that is susceptible to infection by the virus.[33]

Hepatitis C virus

Hepatitis C virus (HCV) belongs to the family *Flaviviridae*, genus *Hepacivirus*, and is the main causative agent of chronic hepatitis. HCV has a linear single-stranded ARN genome consisting of approximately 10,000 positive-sense nucleotides, enveloped, and with an icosahedral symmetry

capsid. Infection is mainly transmitted by the parenteral route, but transmission by sexual contact and vertical transmission may also occur. While the exact risk of a potential vertical transmission from mother to child has not been estimated yet, women with high viremia levels have been seen to be able to infect their offspring,[34] and women co-infected with HCV and HIV-1 have been reported to have a greater increase in the potential for transmitting hepatitis C to their children.[35]

Approximately 150-180 million people worldwide carry the disease, and a 5% rate of transmission of infection by the sexual and vertical routes has only been reported.[36] This has led to controversy about the possibility that HCV may infect semen: while some studies found no virus in semen,[37] others reported the presence of viral genetic material in semen.[38]

It has been postulated that the virus is not able to integrate its genome into seminal cells because it is not a DNA virus, unlike HBV, and has no reverse transcriptase activity, unlike HIV. It should also be reminded that viral levels in seminal plasma change rapidly over time.[38]

Presence of viral RNA in extrahepatic hosts, such as sperm cells and peripheral blood mononuclear cells, such as T and B cells, has questioned the mechanism through which the virus enters the cell. HCV envelope glycoproteins E1 and E2 may mediate entry into the host cell through interaction with their respective receptors. Several viral entry receptors have been reported to date, including CD81, L-SIGN and DC-SIGN, scavenger receptors, low density lipoprotein receptors (LDL-R), and GAG.[39]

CD81 is the most widely reported HCV receptor. It is able to bind to glycoprotein E2, a process modulated by hypervariable regions (HVR-1 and HRV-2) of E2,[40] and has therefore been proposed as the molecule initially binding to viral ligands; however, binding to another unknown receptor is required to achieve HCV entry into the host cell.[40]

Additional candidate receptors for viral adhesion and entry include:

a) Human scavenger receptor class B type I (SR-BI): Scarselli et al found that glycoprotein E2 of HCV was bound to human hepatoma cells which had no CD81 on their surfaces.[41]
b) LDL: It has been postulated that several members of the Flaviviridae family, including HCV, upon binding to certain low density lipoprotein (LDL) particles, are endocytosed through LDL receptors (LDLr), and their entry could end in a productive infection. This was shown by adding anti-LDLr antibodies and blocking the in vitro process of virus entry into several cell types through endocytosis.
c) DC-SIGN: Other molecules that may play a significant role in cell pathogenesis, immunity, and tropism include the calcium-dependent lectins DC-SIGN, previously reported as another potential HIV receptor, and L-SIGN, which is expressed on liver endothelial cells and lymphoid nodules. Both molecules are able to bind to mannose-rich N-glycan particles located on glycoprotein E2 of HCV and act as specific receptors for virus entry into the cell.
d) Heparan sulphate: As previously mentioned for viruses belonging to the *Herpesviridae* family, HSV and HCMV, Barth et al reported that binding between gp E2 of HCV and heparan sulphate located on the cell surface is required for initial interaction of HCV with its target cell. They found that the N-terminal fraction of HVR-1 was positively charged with amino acid residues that may bind to other negatively charged components such as cell surface GAGs.[42]

Although receptors and co-receptors for HCV entry into other body cells have been reported, such receptors have not been reported for cells in semen, which creates a gap in knowledge.

All of these controversies have led to the conclusion that the virus is present in semen at low or undetectable levels depending on the detection method used. This would not represent a high risk of sexual transmission, but may contribute to male infertility because of immune and inflammatory reactions.[35]

Human papillomavirus

Human papillomavirus (HPV), a former member of the *Papovaviridae* family now belonging to the *Papillomaviridae* family, is a naked, double-stranded DNA virus with a capsid with icosahedral symmetry. Almost 100 types of HPV have been identified to date, a third of which are able to infect mucosal and skin epithelial tissues of the anogenital tract and limbs. Such types include PVH-16, 18, 31, 33, 45, 6, 11, among others. HPV is responsible for conditions such as skin warts, anogenital blisters, and cervical cancer. Approximately 10,000 women are diagnosed with cervical cancer worldwide, of which 5,000 die annually.[43]

HPV infection is among the most common STD worldwide, mainly in women. According to the IARC (International Agency for Research on Cancer), more than 18,000 women from 13 countries have been shown to have the viral genome in their cells, and 75% of partners of these women have been infected by this virus.

There is current debate about the possibility that semen may be infected by the virus, and several theories have been proposed. Different studies assessing the presence of HPV in several anatomical sites of the MRS of heterosexual males found the virus to be present in penile basis, glans, scrotum, urethra, semen, and anal region. Several studies have also found the HPV genome to be present in semen samples from patients with penile warts, with infection predominating in the cell fraction of spermatozoa and epithelial cells.[44]

There has been speculation about other receptors, such as the trypsin receptor for PVH-33 in murine cells.[45] Integrin α_6, from the $\alpha_6\beta_4$ integrin complex, has also been suggested to be able to interact with those viral proteins.[46] However, none of these receptors have been related to the cells forming semen, and the mechanism by which the virus enters the cells is therefore still unknown.

Children born with HPV have been reported, but the transmission route in such cases is unknown. Transmission by sexual contact between the parents has been suggested, but this has not been elucidated, because

many of the children had no infection symptoms. It has been suggested that transmission from both the mother and father, i.e. as a hereditary component, may occur from zygote conception. The virus has also been reported to be transmitted by the vertical route because it may infect the birth canal, placenta, and the different fluids coming in contact with the fetus.[47] The viral genome has been found in semen of some men with no symptoms of infectious diseases or blisters in their penises. More specifically, viral DNA fragments are found scattered at the limit of the lower part of the sperm head.[47] Because of this, the chance that these viruses may be inadvertently transmitted not only to the partner, but also to the offspring, is increased because they may become asymptomatic carriers.

Vertical transmission from father to child occurs via semen

Scientific progress in the field of reproductive biology has currently increased the possibility that serum-mismatched couples, particularly those where the male is HIV-positive, may consider having children. At this point it is important to determine the ability of each virus to be stored in semen and transported, either by direct sexual contact or fertilization techniques, not only to the partner, but also to offspring. Molecular techniques such as PCR now allow for simpler identification of the presence or absence of viruses in semen.

Research analyzing HIV-positive patients who had undergone intrauterine insemination procedures after sperm washing showed that both mother and fetus were not seropositive.[48] This suggests that sperm washing "removed" viral particles exposed on the sperm surface.

On the other hand, in addition to the proven ability of HVB to integrate its DNA into the sperm genome to replicate itself and be transported to other cells, oocyte infection by HBV and HCV has occurred in artificial insemination techniques. This suggests that both semen (non-sperm cells and free virus) and spermatozoa are responsible for transport to the oocyte.[49] Several studies evaluated the presence of HCV in semen samples and found very low viral levels. When sperm washing techniques were performed before the fertilization procedures, viral RNA was not found by PCR, and these samples were viable for fertilization and fetal development.[38] According to this, *in vitro* assisted reproduction techniques may be considered safe, provided adequate sperm analysis procedures are used to prevent infection of both oocyte and fetus, possibly by transfer of viral genetic material from semen to the new individual.

As regards neonatal herpes, it has been documented that the fetus may be infected with HSV during pregnancy. This is of special concern because disseminated or central nervous system infections may eventually be fatal in newborns. The risk of acquiring such infections increases when the mother becomes infected at around the third term of pregnancy. Measures to decrease risk factors mainly include sexual of abstinence, reduction of orogenital contacts, and use of condoms.

With regard to HCMV, the British Andrology Society recommended exclusion of sperm donors seropositive for the virus to prevent risk of congenital infection. This recommendation was based on studies identifying high rates of symptomatic congenital infections in newborns caused by positive women and by the presence of this pathogen in semen, showing that the virus does infect the mother and fetus via sperm.[50] Only donors with a recent seroconversion are currently rejected.

Conclusions

The first step required for target cell infection by a virus is adhesion, occurring through proteins and glycoproteins in the viral surface which recognize specific receptors located on the cell surface. Table 1 summarizes the mechanisms of infection, i.e. how the different viruses enter the cells forming semen.

While receptors mediating the adhesion and entry process of HIV into cells having CD4 receptors and co-receptors on their membrane have been defined, this process is still unclear for all other viruses, and several (co)receptors have been postulated as responsible for this step. Most reviewed viruses, including HSV-1 and 2, HCMV, HCV, and HPV, have a common receptor, heparan sulphate, which could be the main mediator in that process by taking care of early adhesion of viral particles to the cell surface.

According to the reviewed studies, offspring may be infected with any viral agent discussed in this monograph. However, the role that would be played by semen, and specifically spermatozoa, as vehicles transporting the virus to the oocyte has not been fully elucidated yet for all viruses.

An additional significant finding for some viruses is the possibility that organs responsible for forming semen such as epididymis, prostate, seminal vesicles, and the different ducts through which they are transported may have epithelial or other cells infected by these viruses. Thus, upon passage of seminal fluid these cells may come into contact with and infect not only plasma, but also sperm. Leukocytes are also found in semen or in the event of any MRS infection may, if they carry the virus, contribute to infection of all other cells in semen and to transport to the oocyte. This suggests that the blood-testis barrier is not in itself a protection system for semen or spermatozoa, because when these leave the seminiferous tubules they are exposed to an environment conducive to infection by many viruses that may originate in the MRS.

Hypotheses postulated in this monograph should be proved or rejected by performing experimental studies to achieve a deeper understanding of the receptors involved in entry of the different viruses into seminal cells and to assess whether viruses are transmitted or not to the offspring upon oocyte fertilization.

Table 1 – Summary: mechanisms of semen infection by viruses

Virus	Ejaculate fraction infected	Mechanism of infection of seminal fraction	Transmission to offspring in semen
HIV-1	Spermatozoa, seminal plasma, and leukocytes	CD4 receptors and co-receptors in immune system cells; other potential receptors in spermatozoa: mannose receptors, DC-SIGN, GAAL	Possible
HSV-1 and HSV-2	Spermatozoa, seminal plasma, epithelial cells of accessory glands and leukocytes	Unknown. Potential binding of virus to receptors on seminal cell surface: heparan sulphate, receptors of the immunoglobulin superfamily, and mannose receptors	Unknown
HCMV	Sperm cells and leukocytes	Unknown. Potential binding of gB to heparan sulphate and other unidentified receptors in sperm cells	Possible
HBV	Spermatozoa and leukocytes	Unknown. Potential binding of envelope protein L to an unknown receptor	Possible
HCV	Spermatozoa and seminal plasma	Unknown. Virus binding to HS and other unidentified receptors in sperm cells: SR-BI is a potential candidate	Possible
HPV	Spermatozoa and seminal plasma	Unknown. Potential binding mediated by HS which interacts with viral L1	Unknown

Funding

This study was supported by the School of Medicine, Universidad de Antioquía, Medellín. Walter Cardona Maya was awarded a scholarship by Colciencias, Colombia.

Conflict of interest

The authors declare no conflict of interest.

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