Journal of Reproductive Immunology 83 (2009) 168–172

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

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

The role of the local microenvironment in regulating susceptibility and immune responses to sexually transmitted viruses in the female genital tract

Charu Kaushic*

Department of Pathology and Molecular Medicine, Center for Gene Therapeutics, Michael G. DeGroote Center for Learning and Discovery Room 4014, McMaster University, 1200 Main Street West, Hamilton, Ontario, Canada L8N 3Z5

ARTICLE INFO

Article history:
Received 27 January 2009
Received in revised form 22 July 2009
Accepted 1 August 2009

Keywords:
Sexually transmitted virus
Genital tract
Epithelial cell
Sex hormones
Immune response

ABSTRACT

Sexually transmitted viruses cause chronic infections that have serious long-term health consequences. Based on the evidence from clinical and epidemiological studies, women carry a disproportionately higher burden of sexually transmitted diseases. The reasons for this are not well understood and possibly relate to a variety of social, behavioral and economic factors. In addition to these factors there are biological reasons that contribute to the higher prevalence in women. In this context it is critical to focus on and understand the local microenvironment of the female genital tract, since the majority of viral infections in women occur by heterosexual transmission. The genital tract is also the target site for initiation and maintenance of protective immune responses that could prevent or eliminate viral infections. The epithelial cells of the genital tract provide the first line of defense against viral entry. The interactions between each sexually transmitted virus and the genital epithelium are distinct and determine the outcome of exposure. They are also influenced by a number of factors in the local genital milieu. Among these factors are the female sex hormones that regulate both the susceptibility as well as immune responses to viral infections in the genital tract. Better understanding of the interactions of viruses with the local environment in the female genital tract will lead to development of novel methods to prevent sexually transmitted infections as well as to enhance innate and adaptive immunity.

1. Introduction

Sexually transmitted diseases (STDs) are among the most prevalent infectious diseases worldwide. While bacterial STDs such as Chlamydia and gonorrhea are curable, sexually transmitted viruses such as genital herpes, HIV-1 and HPV cause incurable lifetime infections. A recent bulletin from the World Health Organization released in 2008, estimated that globally 536 million people aged 15–49 are infected with HSV-2 (Looker et al., 2008). Every year, 23.6 million people in this age group become newly infected with HSV-2. Overall, HSV-2 prevalence was found to be higher among women than men, with the lowest prevalence rate of 13% among West European men and the highest prevalence rate of 70% in sub-Saharan African women. The latest report from UNAIDS estimated 33 million people living with HIV world wide of whom 50% are now women (Unaids, 2008). In fact, the fastest growing phase of this pandemic is currently by heterosexual transmission in women (Unaids, 2008). These and other epidemiological data on bacterial STDs have consistently found that women carry a higher burden of these infections compared to men (Center for Disease Control and Prevention, 2009). While social, economic and behavioural

* Tel.: +1 905 525 9140x22988; fax: +1 905 522 6750.
E-mail address: kaushic@mcmaster.c.

0165-0378/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.jri.2009.08.010

factors contribute to the increased prevalence of sexually transmitted infections in women, less attention has been paid to biological reasons underpinning the increased incidence in women. It is important to realize that biological susceptibility to sexually transmitted viruses is not an absolute determinant, rather it is a continuum. The outcome of viral exposure is determined by the sum total of a number of external and innate factors. These include but are not limited to genetic susceptibility (or resistance), "infectiousness" and load of the virus in the inoculum, presence of other co-infections and innate mechanisms such as genital microflora of the host. Additionally, the local microenvironment in the reproductive tract, where these viruses initiate transmission, itself has a profound influence on the outcome of exposure. This review will focus on two important factors in the local milieu of the female genital tract that could significantly affect the outcome of sexually transmitted viral infections. These are the interactions of viruses with the epithelial lining of the female genital tract and the influence of sex hormones on the susceptibility and immune responses to sexually transmitted viruses. I will review work from our group and others, focusing mainly on HSV-2 and HIV-1, and conclude with some of the implications for prophylactic and therapeutic strategies.

2. Characteristics of the mucosal lining of the female genital tract

Epithelial cells that make up the mucosal lining of the genital tract are the first barrier against sexually transmitted pathogens. Viruses can be transmitted sexually across both the lower and upper reproductive tract epithelium. The epithelial lining and the underlying stroma in the reproductive tract of women undergo dynamic changes during the menstrual cycle as well as throughout the life time of women. The lower reproductive tract in women is composed of the ectocervix and the vaginal tract. The mucosal lining here consists of stratified squamous epithelium that can be more than 25 cell layers thick (Miller et al., 2000). In contrast, the upper reproductive tract, made up of the endocervix and endometrium, are composed of a single layer of columnar epithelium that rest on a continuous, thin basement membrane (Coombs et al., 2003). The columnar epithelium is characterized by the presence of tight junctions between cells that make it impermeable to entry of any large molecules and particulate matter, including pathogens. The thick stratified epithelium of the lower reproductive tract, although not impermeable, is robust and provides a substantive physical barrier compared to the delicate single layer of columnar epithelium of the upper reproductive tract. Both the columnar and squamous epithelium are exquisitely responsive to, and functionally regulated by reproductive hormones, estradiol and progesterone (Wira et al., 1999). From an immunological point of view, the lower reproductive tract is exposed to the external environment, as well as commensal flora. Therefore, epithelial cells lining the lower tract must constantly differentiate between commensal flora and pathogens. The epithelium of the endometrium, on the other hand, lacks direct contact with the external environment and is characterized by absence of commensal flora. Rather, its function is primarily reproductive, serving as a site for implantation and development of the fetus. The squamo-columnar junction between the ectocervix and the endocervix where the squamous epithelium abruptly changes to the single layer of columnar epithelium, called the transitional or transformation zone, is the most vulnerable point in the genital epithelium and an easy target as an entry point for pathogens such as HIV-1. In fact, presence of ectopy (the protrusion of the cervical transformation zone outside the external os) of the cervix has been associated with increased risk of heterosexual transmission of HIV-1 (Moss et al., 1991). Immunologically, the transformation zone is the most active site in the reproductive tract; lymphocytes and antigen presenting cells are present in abundance in normal women and further increased during inflammatory conditions (Pudney et al., 2005).

3. Interactions of the genital epithelium with sexually transmitted viruses

While all sexually transmitted viruses have to cross the obstacle of the female genital epithelium to cause a productive infection in the host, their specific interactions with the epithelial lining in the genital tract are quite different. Herpes simplex virus type 2 (HSV-2) directly infects the genital epithelium and undergoes replication within it (Corey and Wald, 1999). It then infects adjacent epithelial cells and other cell types located under the epithelium, subsequently infecting peripheral nerves where it can become latent. The latent virus re-activates from time to time to replicate, is shed in the genital tract secretions leading to further transmission. The consequence of direct infection and replication in the genital epithelium is evident in the efficiency of transmission of HSV-2. Roughly one in every 4 or 5 sexually active adults is infected by HSV-2 in North America (Paz-Bailey et al., 2007). On the other hand, the interaction of HIV-1 with the genital epithelium is still not completely understood (Coombs et al., 2003; Miller and Shattock, 2003). Unlike HSV-2, it has a comparatively poor rate of transmission (1:200 to 1:1000 for each exposure) (Quinn et al., 2000). This makes the likelihood of productive infection in genital epithelium unlikely. However, studies done in this area have been far from conclusive.

Early in vitro studies indicated that genital tract epithelial cell lines could be infected by HIV (Philips and Bourinbaiar, 1992). The X4-tropic strain of HIV (T-tropic) was shown to replicate in cultured human primary uterine cells, however the R5-tropic strain (macrophage-tropic) was taken up and released from the cells, unmodified (Asin et al., 2004). Over the years, the demonstration of alternative cellular receptors, such as Gal-Cer, C-type lectins such as DC-SIGN, mannose receptors, proteoglycans such as heparin sulfate and syndecan that bind to HIV have raised the possibility that virus could get into mucosal epithelial cells using these alternative receptors (Bobardt et al., 2007; Geijtenbeek et al., 2000; Philips and Bourinbaiar, 1992; Stoddard et al., 2007; Turville et al., 2002). More recently, the organ culture models of intestine, tonsil and cervix have been able to add relevant information regarding HIV transmission across epithelium (Hladik et al., 2007; Maher et al., 2005a,b). These studies indicate that HIV-1