



Commentary

Immune landscape of female reproductive tract and HIV susceptibility

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Hormonal changes during the menstrual cycle are associated with changes within the immune system and susceptibility to HIV infection. There are two phases of the menstrual cycle in the female reproductive tract (FRT): follicular or luteal. However, which phase is more susceptible to HIV infection remains controversial. Therefore, a more detailed understanding of the relationship between the menstrual cycle and immune response can provide insight into their role in the sexual transmission of HIV, a subject of intense current study [1].

A previous study compared follicular and luteal mucosal markers of HIV susceptibility in healthy women [2]. This study included not only vaginal tissue gene expression profiles as a function of differences in the vaginal immune cell populations but also the antimicrobial effects of the cervicovaginal (CV) lavage (CVL) and vaginal flora on the above parameters. CV tissue was also biopsied during the follicular and luteal phases of the menstrual cycle to determine whether differences could be identified prior to challenge with HIV *ex vivo* that influenced susceptibility and found no statistical differences of mucosal markers during the follicular and luteal phase [2]. To characterize immune cell populations that generally reside within these tissues, samples from the lower female genital tract (FGT) of healthy HIV-negative women were utilized [3]. Paired CVL and blood samples were taken at different points throughout their menstrual cycle and found that mucosal T cells in the lower FGT were predominantly CD4+ T cells expressing the cytokine receptor CCR7 -an marker of the chemotactic ability of these cells. Additionally, the co-expression of HIV susceptibility makers such as CCR5 and CCR38 were significantly upregulated in FGT CD4+ T cells compared to those expressed by corresponding CD4+ T cells in blood samples. These findings reveal the susceptibility of these cells to HIV and their potential to travel via the chemotactic response between the mucosal epithelium of FGT and peripheral lymphoid tissues [3].

These findings are further supported by results obtained in studies of repeated low-dose vaginal exposure of SIV/SHIV in macaque models that have led to the characterization of fluctuation in viral

susceptibility during the late and luteal phase of the menstrual cycle [4,5]. In one study, nineteen animals were vaginally challenged with repeated low-dose SHIV exposures throughout the study. These exposures were terminated after the macaques displayed the initial signs of viremia. Eighteen macaques began to show signs of viremia during the follicular phase of their menstrual cycle, compared with one macaque that started to display signs of viremia during the luteal phase. The median number of viral challenges was four for detecting the virus in the follicular phase versus ten for the animal that showed initial viremia during the luteal phase [4]. Similar observations were reported from a cohort of thirty-seven sex workers from Nairobi, Kenya [6]. In this study, cervical mononuclear cells were collected using a swab of the vaginal vault, cervical spatula scraping of the ectocervix, and cervical brush scraping of the endocervix. Genital inflammation was defined as the presence of chemokines, namely CCL3, CCL4, CXCL10, and CXCL8 above the upper quartile level. Throughout the study, plasma progesterone levels increased an average of seven-fold, and oestradiol levels were elevated during the luteal phase. In addition, the proportion of CD4+ T cells expressing CCR5 and CD69 were found to be more susceptible to HIV during the follicular phase. This increased susceptibility of CD4+ T cells correlated with an increased level of CCL2, a chemokine suggestive of inflammation [6]. These data establish the fact that menstrual cycles are associated with changes within the immune system.

The recent investigation by Swaims-Kohlmeier and colleagues further provides testimony to this notion. They describe the relationship between the menstrual cycle and immune system, specifically related to CD4 T cells and progesterone activity, using pigtail macaque models, as well as human blood and cervical samples [1]. They have shown that the late luteal phase of the menstrual cycle decreases progesterone levels as the next menses approaches. Further, they found that the menstrual cycle is linked to a type-1 specific immune response that may increase HIV susceptibility during the late luteal phase. Increased CCR5 expression was observed in both the circulating CD4 T cells and those present within the FRT during the late luteal phase, leads to T-cell recruitment and changes within the FRT. In addition, there is increased production of proinflammatory cytokines, including IFN- γ and TNF- α , which contribute to the mounted immune response. Since CCR5 is a co-receptor for HIV and CD4 cells are well-known targets for HIV infection, increased CCR5 expressing CD4 cells in the FRT in the late luteal phase could enhance HIV infection rates [1].

Therefore, future studies aimed at addressing details of the inflammatory properties of CD4 T cells that include examination of

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the expression of integrins $\alpha 4\beta 7$, that can mediate trafficking and play a role in infection and susceptibility, are warranted [7]. More research is needed on studies that utilize synthetic menstrual cycle regulation methods, such as progesterone-based contraception, and how that may affect progesterone levels, immune response, and HIV susceptibility. In addition, studying the conditions and/or diseases localized within the FRT that can potentially influence the inflammatory and immune response in the vaginal zone irrespective of progesterone level may provide unique insights. Therefore, future studies utilizing multi-omics analysis of the FRT could reveal immunometabolic dysfunction of the CD4+ T cells and its involvement in enhancing HIV infection [8].

Contributors

SNB solely wrote this commissioned commentary.

Declaration of Competing Interest

The author declares no conflicts of interest.

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