Proteomic analysis of cervicovaginal fluid uncovers immune pathway variation between the follicular and luteal phases of the menstrual cycle - implications for HIV susceptibility

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BACKGROUND

Young women bare the greatest HIV burden when considering prevalence, fatality and susceptibility. Heterosexual intercourse is the main route of new infections, making the mucosa of the female genital tract (FGT) the first site of contact for male to female HIV-1 transmission. Although this surface has physical and biological defense barriers, HIV is still able to establish infection.

It has been postulated that the defensive capacity of the FGT fluctuates over the course of the hormonally governed menstrual cycle such that there are specific times of increased vulnerability to infection.

The progesterone-dominant luteal phase, the period after which a woman has ovulated up until menstruation, and injectable progestin-based contraceptives have been associated with an increased susceptibility to SHIV and HIV infection in non-human primate models, human explant tissue studies, and serodiscordant couple studies, respectively.

The mucosa of the FGT contains a plethora of secreted immune factors capable of both inhibiting menstrual cycle2,9 and some factors associated with HIV resistance and inhibition have been found and serodiscordant couple studies6 respectively.

RESULTS

Of the 525 unique proteins identified using label-free mass-spectrometry based proteomics, 47 (22 immune factors) were found to be differentially abundant based on menstrual phase (Student T-test p<0.05, >2 fold change).

Figure 1. An overview of the natural defense barriers present in female genital tract. The FGT possesses physical barriers that help to protect from infection such as a stratified epithelium found in the ectocervix and vagina, and a mucous plug in the endocervix. The FGT also has biological barriers that pathogens must overcome such as the acidic environment in the lower FGT created by the resident Lactobacillus microflora, the immune cells found throughout the subepithelium, and the antimicrobial factors that secrete into the mucosa itself.

This study demonstrates that there are significant differences between the proteomes of women in the follicular phase and those in the luteal phase of their menstrual cycles.

Factors enriched during the follicular phase were primarily associated with cell proliferation and differentiation, cell-cell adhesion, and peptidase inhibition which may help to create a more protective environment against infection as these biofunctions contribute to a healthy, immune regulated epithelium.

Factors enriched during the luteal phase were primarily associated with chemotaxis and activation of immune cells including HIV target cells such as T lymphocytes, peptide activity, cell permeability, viral infection and even HIV infection specifically. Many of the proteins found to be overabundant during the luteal phase were also highly associated with one another with many co-expressing at the same time suggesting that they may be regulated by a common upstream regulator or pathway.

This study may help to explain why women may be more susceptible to HIV infection during the luteal phase of their menstrual cycles or possibly through the use of exogenous progesterone such as what is found in some hormonal contraceptives as the findings of this study demonstrates that the proteomic profile of the luteal phase generates an environment that could be more conducive to successful HIV infection. However, further studies to confirm this possibility are required.

The most important implications and applications of the findings this study and its further investigation may be the potential discontinuation of progesterone based hormonal contraceptives particularly for populations at high risk of HIV acquisition.

METHODS

This study used an unbiased proteomics approach to uncover immune pathway variation between the follicular and luteal phases of the menstrual cycle.

CONCLUSIONS & FUTURE DIRECTIONS

REFERENCES & ACKNOWLEDGEMENTS