Double infection by HSV-2 and HIV: how does HSV-2 infection facilitate for HIV infection?

Berichterstattung

Projektinformationen

APO-HSV-2/HIV

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Projekt abgeschlossen

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Dieses Projekt findet Erwähnung in ...

Final Report Summary - APO-HSV-2/HIV (Double infection by HSV-2 and HIV: how does HSV-2 infection facilitate for HIV infection?)

EIF Marie Curie Action project No 221246
'Double infection by HSV-2 and HIV: how does HSV-2 infection facilitate for HIV infection'

Genital herpes is the main cause of genital ulcers worldwide; the prevalence of herpes simplex virus (HSV) type 2 infections in general populations ranges from 10 % to 60 %. Disruption of the integrity of the vaginal mucosa, which results from sexually transmitted diseases (STDs), such as herpes simplex virus infection, heightens the risk of HIV transmission.

There are several types of cell death, of which apoptosis is a physiological process necessary for vaginal epithelium turnover during an oestrous cycle. Fas is a receptor belonging to the TNF receptor family which has been showed to participate in vaginal regression during an oestrous cycle. Considering the fact that disruption of the integrity of the vaginal mucosa resulting from HSV-2 heightens the risk of HIV transmission, the aim of this project was to test how apoptosis during HSV-2 infection may add to disruption of vagina epithelium integrity.

In particular, the research goals included:
(i) checking whether HSV-2 infection can lead to apoptosis and disruption of the vaginal mucosa,
(ii) contribution of Fas and other receptors of the TNF family to vaginal epithelium lesions during HSV-2 infection and
(iii) influence of HSV-2 infection in susceptibility to HIV-1 infection.

The project used two models of HSV-2 infection: in vitro model of HSV-2 epithelial infection - mouse keratinocyte 03C cell line and mouse epithelial Hepa 1-6 cell line and in vivo herpes genitalis model in C57BL mice. Despite up-regulation of Fas and FasL, HSV-2 infected keratinocytes and epithelial cells (in vitro model) showed a moderate level of apoptosis during infection due to the up-regulated expression of the anti-apoptotic factors Bcl-2, Akt kinase and NF-kB.

The experiments performed in vivo, in intra-vaginally infected C57BL mice, showed the presence of apoptotic HSV-2 infected and uninfected cells. Inflammatory lesions within the HSV-2 infected epithelium of C57BL6 mice consisted of the infected cells up-regulating Fas, FasL and Bcl-2, and uninfected cells up-regulating Fas.

To assess the role of Fas in lesion development during genital HSV-2 infection, we applied a well-established HSV-2 model to MRL-Faslpr/J (Fas-/-) and C3-Faslgld/J (FasL-/-) C57BL6 mice. HSV-2 infection of Fas and FasL deficient mice led to increased apoptosis and stronger recruitment of neutrophils within the infection sites. Therefore, the lack of the functional Fas or FasL gene led to development of larger vaginal lesions.

On the basis of this project, we conclude that HSV-2 infection leads to exacerbation of apoptosis and inflammatory processes. HSV-2-infected cells of the vaginal epithelium are resistant to Fas/FasL-induced apoptosis, but this cell death pathway participates in the regulation of inflammatory response in the vaginal epithelium at the initial stage of HSV-2 infection.

Globally, more than 40 million people are currently infected with HIV-1, with the vast majority of infections initiated at mucosal surfaces. Heterosexual transmission accounts for the majority of new HIV infections and approximately half of the people now living globally with HIV are women. Sexually transmitted diseases, such as HSV-2 not only increase the risk of HIV-1 transmission, they also increase its effective spreading.

Development of intra-vaginal topical formulations of antiviral agents may provide a solution in the absence of effective, affordable anti-HIV prophylactic therapy. The cellular and immune mechanisms that govern maintenance of the vaginal epithelium integrity, such as Fas/FasL, provide a novel possibility for production of such microbicides.

Contact: francesca.chiodi@ki.se, krzyzowskam@yahoo.com

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