

NEWS AND COMMENTARY

Interferon epsilon and HIV

Expanding role for type I Interferons in restricting HIV growth

Stephen J Kent and Anthony D Kelleher

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The process of HIV infection through the female genital tract is relatively inefficient at an estimated 1 infection per 1000 coital acts.¹ Despite donor semen samples having a large array of different HIV strains, when infection does occur, typically only one strain initiates the infection in the recipient.² This 'restriction' in HIV infection and growth is the subject of intense research since it should reveal new vulnerabilities of HIV, and potential modalities to prevent or treat HIV.

The field has focussed for some time on the type I interferons alpha and beta as candidate molecules that affect HIV transmission. Hahn's group recently showed HIV strains that are transmitted through the mucosa to cause infection were much less susceptible to the inhibitory effects of interferon (IFN)- α 2 and IFN- β than strains that did not cause infection³—that is—the strains successful in initiating a new infection were able to survive this first wave of innate immunity. IFN- α 2 also reduces the susceptibility of monkeys to simian immunodeficiency virus (SIV) infection.⁴ The inefficiency of HIV transmission seems at least in part related to local innate immune responses in the female genital tract.

Hertzog's group at Monash University recently identified IFN- ϵ as a new and important type I IFN expressed in the female genital tract in both mice and humans.⁵ Using IFN- ϵ knockout mice, the group showed convincingly that IFN- ϵ plays a role in the protection of mice from female genital tract infections with a herpes simplex virus and a Chlamydia strain. IFN- ϵ could thus also play a role in preventing or modulating infection with HIV, a highly relevant area to explore (Figure 1).

Together with Mak's group at Deakin University they now show in this issue of *Immunology and Cell Biology* that IFN- ϵ induces the expression of a series of known HIV restriction factors *in vitro* in both T-cell lines and primary T cells.⁶ The level of restriction factor upregulation was broadly similar to that induced by another type I interferon, IFN- α . IFN- ϵ also reduced the *in vitro* replication of HIV both in T-cell lines and primary T cells. The level of HIV replication inhibition induced by IFN- ϵ was similar to that induced by IFN- α , but somewhat less than that of IFN- β . Through using a HIV strain deficient in the *vpu* gene that is important for virus release, the authors show that IFN- ϵ does not significantly inhibit virion release *in vitro*. Interestingly, HIV that was generated under IFN- ϵ treatment was several fold less infectious than HIV produced in the absence of IFN- ϵ exposure.

Taken together, the findings in this report are consistent with the ability of IFN- ϵ to reduce HIV replication *in vitro*. It is certainly plausible that IFN- ϵ , which is expressed primarily in the female genital tract, plays a role in knocking down HIV replication at this portal of entry and reducing transmission.

Several future studies are suggested by this work. Experiments that examine the

susceptibility of macaques to SIV in the setting of IFN- ϵ treatment may help confirm the relevance of these findings. Similarly, examining transmitted HIV viruses, in comparison to non-transmitted strains from the same donor, for their susceptibility to IFN- ϵ suppression would be of interest since it is possible that IFN- ϵ is an additional important factor involved in the 'bottleneck' of HIV strains transmitted. Further dissection of the steps in the HIV life cycle that IFN- ϵ inhibits may reveal new targets for type I interferons and virus suppression.

IFN- ϵ is expressed in the female reproductive tract in a hormone-dependent manner, with peak expression during the proliferative phase of the menstrual cycle when estrogen levels are high. Levels of IFN- ϵ in the female reproductive tract are much lower in the secretory phase of the menstrual cycle when progesterone levels are higher. Long-acting contraceptives, which generate higher levels of progesterone, are a risk factor for HIV transmission in humans and SIV infection of monkeys.⁷ While high levels of progesterone have multiple effects that could affect HIV transmission, including thinning the vaginal mucosa layers, hormone-induced reduction in IFN- ϵ could be playing a role in the propensity of long-acting contraceptives to promote HIV transmission.

In summary, there is a new kid on the type I IFN block that can reduce HIV replication. The expression of IFN- ϵ in the female genital tract and previous murine studies on other sexually transmitted infections suggest that it could play an important role in modulating HIV transmission to females.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SJ Kent is at ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, The University of Melbourne, Melbourne, Victoria, Australia; Department of Microbiology and Immunology, Peter Doherty Institute for Infection and Immunity, The University of Melbourne, Melbourne, Victoria, Australia; Department of Infectious Diseases, Melbourne Sexual Health Centre, Alfred Health, Central Clinical School, Monash University, Melbourne, Victoria, Australia and AD Kelleher is at Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia; St Vincent's Centre for Applied Medical Research, Darlinghurst, New South Wales, Australia
E-mail: skent@unimelb.edu.au

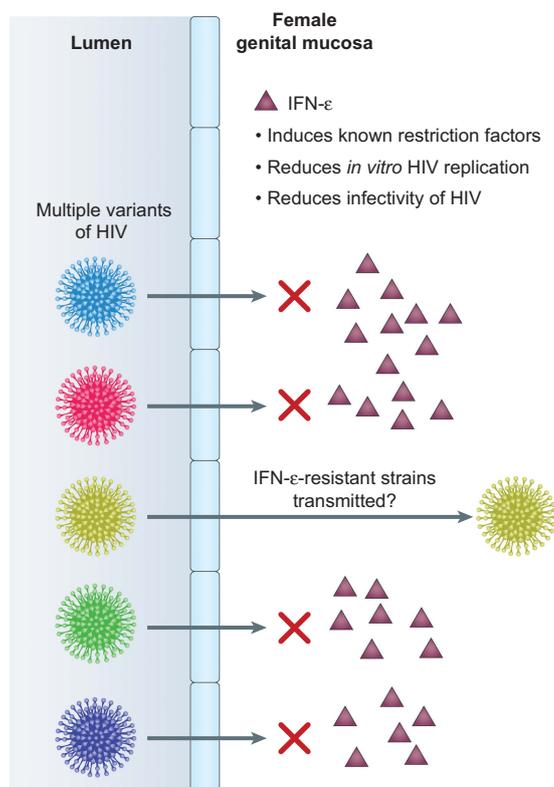


Figure 1 IFN- ϵ may limit HIV infectivity. Upon infection with multiple strains of HIV, production of IFN- ϵ may contribute to the restriction that leads to a single strain infection. IFN- ϵ acts by inducing restriction factors, inhibiting HIV replication and reducing infectivity.

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