

Alloimmune responses and resistance against HIV infection with

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What are alloimmune responses and why are they studied in the context of HIV-1 infection?

Wim Jennes: The alloimmune response refers to the recognition of antigens expressed on the surface of cells from non-self origin (1). Alloimmune responses are induced upon blood transfusion, organ transplantation, sexual intercourse, or during pregnancy. Immune reactivity against allogeneic antigens occurs as a result of differences in major histocompatibility complex (MHC) molecules expressed on foreign cells. MHC molecules, named human leukocyte antigens (HLA) in humans, are encoded by a cluster of extremely polymorphic genes, and no two subjects (except monozygotic twins) display an identical set of MHC alleles.

Alloimmune responses are thought to be protective against infection with the human immunodeficiency virus (HIV) because of several prior observations (2). Macaques immunized with uninfected human cells are protected against a challenge with simian immunodeficiency virus (SIV) grown in the same

human cells. Sexual partners with disparate MHC allele profiles, potentially resulting in strong alloimmune responses, less likely transmit HIV. Also, MHC molecules expressed on infected host cells are incorporated into HIV virions, and viral gp120 and MHC share a degree of homology potentially leading to cross-reactive immune responses. Thus, theoretically, alloimmune responses could protect against HIV infection by rejecting HIV-infected donor cells before virus production can occur, or by targeting MHC and gp120 molecules on free donor virus.

In a recent study, we tested whether subjects resistant to HIV infection have increased levels of alloimmune responses (3). We explored this possibility in Abidjan, Côte d'Ivoire in a population of female sex workers who remained HIV-seronegative despite more than three years of frequent high-risk sexual exposure, in comparison with a group of low-risk HIV-seronegative female blood donors.

How did you measure alloimmune responses and what did you find?

Wim Jennes: Female sex workers in Abidjan, Côte d'Ivoire have frequent unprotected sexual contacts with large numbers of male clients. This results in exposure to a wide range of foreign cells carrying many different MHC molecules. In an attempt to mimic this condition *in vitro*, we stimulated white blood cells

from female sex workers and low-risk female controls with a mixture of inactivated white blood cells from a large group of male controls. We then measured the levels of *in vitro* lymphocyte activation (CD69 expression by flow cytometry) and cytokine and β -chemokine secretion (by ELISA) in both groups (3).

Surprisingly, we found that HIV-exposed seronegative female sex workers showed significantly lower levels of lymphocyte activation and cytokine and β -chemokine secretion after *in vitro* alloimmune stimulation than low-risk female controls. We

noted that cellular alloimmune responses were most suppressed among female sex workers who reported the highest frequencies of unprotected sex. We also measured levels of anti-MHC class I alloantibodies in female sex workers and controls but did not observe any difference (3).

What are the implications of these findings?

Wim Jennes: Our data first of all suggest that repeated unprotected sexual intercourse with multiple partners results in suppression rather than activation of cellular alloimmune responses. This is controversial since one other recent study found exactly the opposite (4). Nevertheless, in the light of our current understanding of human reproduction, our data make more sense. To facilitate pregnancy, the female immune system needs to be tolerant to paternal MHC antigens on semen and on the developing foetus. Indeed, successful pregnancy has been found to be associated with repeated

prior exposure to semen, which induces a state of active local tolerance towards male alloantigens in the female genital tract (5,6). It has been hypothesised that such reproduction-driven immune tolerance in the female genital tract also has a cost, as witnessed by the lack of rejection of human papilloma virus-infected cells during the development of cervical cancer (7,8). Thus, our data do not confirm the hypothesis that highly HIV-exposed but seronegative subjects could be protected against HIV infection by activated alloimmune responses.

Do you believe that suppressed cellular alloimmune responses could play a role in protection against HIV infection?

Wim Jennes: Progressive HIV infection and AIDS are characterised by excessive immune activation, driven by both viral and host factors. It has been observed that *in vitro* allostimulation renders PBMC more susceptible to HIV infection, and that blood transfusion to HIV patients further increases plasma viral load levels. In contrast, low levels of immune activation are a key feature of nonpathogenic SIV infection of natural primate hosts, and contribute

to low HIV susceptibility in humans. Down-regulation of alloimmune responses in HIV-exposed seronegative female sex workers could help maintaining such a low immune activation state, for instance in the female genital tract. Thus, it is at least tempting to speculate that suppressed alloimmune responses, on its own or together with other anti-HIV mechanisms, contribute to protection against infection with HIV.

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