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Commentary

Seminal analyses of HIV-1 transmission

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Semen is the commonest source of transmitted HIV-1 (1-3): an effective vaccine should therefore protect against seminal transmission. HIV-1-vaccine development comprises longstanding efforts to elicit broadly active neutralizing antibodies, bNAbs, through immunisation with the viral trimeric envelope glycoprotein, Env (4). Such antibodies neutralise viral infectivity by binding to functional Env spikes on the outside of the virus and thereby blocking its entry, by membrane fusion, into susceptible cells that express the CD4 receptor and a co-receptor, usually CCR5 (5). Also, passive immunisation, *i.e.*, parenteral administration of bNAbs, is pursued both as therapy and for prevention (6).

Yet, experiments on neutralisation *in vitro* and on protection from infection after challenge with the virus *in vivo* in animal models have not used virus derived from semen. Might the forms of virus in semen differ from experimental virus such that the model results misrepresent what is required for protection in the most common setting for transmission in the real world?

In a study published in *EBioMedicine*, Cavarelli and colleagues describe experiments that contribute to answering such questions (7). The authors infected male cynomolgus macaques with SHIV-162P3, a hybrid virus that has the envelope glycoprotein (Env) from an HIV-1 isolate, adapted to useing macaque CD4, on the surface of the virus particles and the components from a simian immunodeficiency virus inside the virions, thereby rendering them capable of infecting and replicating in the macaque organism, as well as of being neutralised by HIV-1-specific bNAbs (3). The authors obtained splenocytes and semen leukocytes from these monkeys, during acute infection with high levels of virus. They showed that the splenocytes, which allowed more experimentation because of their greater abundance, could mediate intravaginal infection of macaques, as simian immunodeficeincy virus-infected cells have previously been shown to do (8). They then used these infected splenocytes *in vitro* to optimise assays for cell-mediated infection and measured its inhibition by a panel of bNAbs. They also compared the potency and extent of the inhibition with that of infection mediated by cell-free virus particles of the same isolate. Two different kinds of target cells were used in the infection assays: engineered epithelial TZM-bl cells and the more natural peripheral blood mononuclear cells. Well-known bNAbs directed to epitopes on different parts of the Env spikes blocked infection alone and in combination, with varying potency and efficacy. One of them, 10−1074, directed to the base of the V3 region and associated glycans on Env, was selected for the ultimate test with the scarcer infected semen leukocytes. This antibody, which is approved for testing in clinical trials (6), strongly blocked infection mediated by the infected semen leukocytes (7).

One mechanism for cell-mediated infection was first discovered for another retrovirus: human T-cell leukaemia virus type 1 (HTLV-1), but it also applies to HIV-1 (9, 10). An infected cell forms a junction with an uninfected one, sealing off a space through which viral particles are delivered. Since this cellular structure resembles the immunological synapse, which is created when dendritic cells present antigen to T-cells, it was dubbed the virological synapse (9, 10). Several studies have shown that infection by this mechanism requires higher concentrations of bNAbs for blocking than does infection mediated by cell-free HIV-1 particles (3, 10). Indeed, Cavarelli and colleagues also found such a difference (7).

Why are then bNAbs less active against infection via the virological synapse than against free virus particles? Many explanations have been proposed (10). First, synaptic infection is highly effective, yielding high multiplicities of infection in the target cell. This necessitates careful quantification such that the two modes are on an equal footing by yielding similar degrees of infection, as performed by Cavarelli and colleagues (3, 7). Other explanations invoke differences amongst the viral proteins and their interactions in the two contexts, the cell types used for producing cell-free and cell-associated virus, sterically restricted access for the bNAbs, and the influence of multiple participating host-cell proteins (10). The latter effect could be particularly relevant in the current context and raise questions whether virological synapses formed between infected semen leukocytes and uninfected target cells differ qualitatively, thereby conferring differential sensitivity on bNAbs (3, 10). It is hence significant that Cavarelli and colleagues found that the infection mediated by semen leukocytes is at the very least as sensitive to inhibition by bNAbs as that mediated by splenocytes (7).

Arguably, both the potency - IC_{50}, IC_{90}, etc. - and the efficacy - the maximum extent of the reduction in infectivity - influence the capacity of bNAbs to prevent HIV-1 transmission (5). Indeed, neutralisation of infection mediated by cell-to-cell transfer is not only less potent

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but also less effective than that mediated by cell-free virions, specifically for such viral variants as are responsible for sexual transmission from one infected person and the foundation of infection in another (T/F variants, 1, 3, 10). In which regards do such viral variants differ from others isolated from the infected organism?

Stochastic as well as fitness-selection bottlenecks occur in HIV-1 infection, both in the donor and recipient host (1-3). That single lineages are usually transmitted and disseminated is strong evidence for bottlenecks but does not differentiate amongst the mechanisms or stages of restriction (1, 3). The fitness barrier varies and is lowered by inflammation due to genital infections; it is lower for male-to-female than for female-to-male transmission; indeed, when it is substantially lowered multiple lineages can get transmitted (1).

Which viral phenotypic traits are then enriched by the narrowest bottlenecks? Overwhelmingly, T/F viruses are R5 T cell−tropic: they use CCR5 as a co-receptor rather than CXCR4 and require high CD4 densities on the target cells (1). Env of T/F viruses is often less glycosylated than that from other isolates, or it lacks glycans at specific sites (1-3). Factors yielding less glycosylation may include the initial absence of selective NAb pressure in the recipient – the glycan shield then expands again under the selection pressure of the emerging autologous NAb responses – as well as the greater binding of restrictive lectins to the more glycosylated forms in the transmission fluids and at ports of entry (1, 4). T/F viruses studied as infectious molecular clones rather than as pseudoviruses tend to have elevated numbers of Env spikes on virions, thereby enhancing their capacity to attach to and fuse with susceptible cells. All other things being equal, that would lead to a requirement for higher occupancy by neutralizing antibodies to achieve neutralization, although the avidity of the NAbs would also increase (5). Furthermore, T/F viruses are relatively resistant to type 1 interferon (2, 3). But the causal relationships are complicated by how this resistance correlates with mutations that affect intrinsic replication fitness and escape from cytotoxic T lymphocytes (1, 3)

The veracity of extrapolations from HIV-1 animal models to protection of humans by active and passive immunisation depends on how well the biological features of transmission are mimicked experimentally. The finding that bNAbs can block infection mediated by semen leukocytes is a significant step towards such fidelity (7).

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