ANTIVIRALS

Helping hand for HIV

Major efforts have been made to develop agents that prevent the transmission of HIV, but so far, none has been as successful as hoped. Kirchhoff and colleagues now present data showing that semen-derived amyloid fibrils greatly enhance HIV infection. Targeting the formation of these amyloid fibrils from their precursor, prostatic acidic phosphatase (PAP), or blocking their enhancing activity could represent a fresh preventive strategy for HIV.

The authors identified the fibril-forming PAP fragments by screening a complex peptide/protein library of human semen for factors involved in the transmission of HIV. One fraction that enhanced HIV infection in $CD4^+$ T cells *in vitro* contained fragments of PAP. Driven partly by the knowledge that amyloid fibrils associated with Alzheimer's disease enhance HIV infection, the authors used structural analyses to confirm that the PAP fragments also formed amyloid fibrils that they termed semen-derived enhancer of virus infection (SEVI).

In vitro experiments indicated that SEVI enhanced HIV virion binding and fusion to target cells. Enhancement of HIV virion fusion was blocked when cells infected with SEVI-treated HIV were incubated with the fusion inhibitor T20 or a chemokine (C-C motif) receptor 5 (CCR5) antagonist, indicating that SEVI does not bypass HIV's need for a co-receptor to enter a target cell.

Further investigation showed that SEVI amplified HIV infection of $CD4^+$ T cells *in vitro*, with the magnitude of the enhancing effects being highest when the levels of infectious virus were low. SEVI also amplified infection of macrophages and increased *trans*-HIV infection of $CD4^+$ T cells by an epithelial cell line and primary dendritic cells *in vitro*.

In vivo, SEVI significantly enhanced HIV infection of transgenic rats that express human CD4 and CCR5 on T cells and macrophages. *Ex vivo,* infection of tonsillar tissues with very low doses of HIV occurred only in the presence of SEVI. Finally, the authors showed that seminal fluid and semen also enhance HIV infection, possibly due to PAP fragments forming amyloid aggregates.

Overall, Kirchhoff and colleagues show that semen and SEVI enhance infection by HIV, particularly at low viral titres, resembling the conditions of sexual HIV transmission. This was most notable when peripheral blood mononuclear cell cultures and *ex vivo* tonsillar tissues were infected at low viral doses only in the presence of SEVI.

New HIV prevention strategies could be developed by blocking the generation of SEVI, possibly by targeting PAP, or by inhibiting the enhancing ability of SEVI. As SEVI is a type of amyloid fibril, research into therapeutic strategies against human amyloid diseases might be applied to the design of therapeutic agents against amyloid aggregates.

Bethan Hughes

ORIGINAL RESEARCH PAPER Münch, J. *et al.* Semen-derived amyloid fibrils drastically enhance HIV infection. *Cell* **131**, 1059–1071 (2007)
FURTHER READING Flexner, C. *et al.* HIV drug development: the next 25 years. *Nature Rev. Drug Discov.* **6**, 959–966 (2007) | Sacchettini, J. C. and Kelly, J. W. Therapeutic strategies for human amyloid diseases. *Nature Rev. Drug Discov.* **1**, 267–275 (2002)