Direct cell to cell transmission of HIV confers resistance to therapy and may produce a virus reservoir

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Direct cell to cell transmission of HIV has been shown to be an efficient form of infection, bypassing cell-free virus loss[1] during the process of finding a new cell to infect. Though direct cell to cell infection is not thought to physically protect HIV from the effects of drugs used in anti-retroviral therapy, we observed that direct cell to cell transmission is much less sensitive to drugs relative to infection with free virus, a result explained by a probabilistic model of infection. In the presence of insufficient therapy, cell to cell infection may form a reservoir of ongoing replication.

I. Purpose

The classical description of virus transmission, which assumes radiation-like absorption of cell-free viruses by susceptible target cells, does not take account of directed virus transmission between infected donor and uninfected target cells, observed for many viruses. Unlike cell-free virus infection, which is accurately described by a Poisson process[2], direct cell to cell transmission of HIV has been shown to result in local high concentrations of transmitted virus between the infected donor and uninfected target cells[3-8]. Direct cell to cell infection is not thought to physically protect the virus from the effects of drugs used in anti-retroviral therapy, since almost all drug types act downstream of entry[9]. We investigated whether directed transmission would nevertheless increase the probability of successful infection in the presence of anti-retroviral drugs.

II. Results

We infected target cells with either cell-free HIV or previously infected donor cells, which can infect new cells by both the cell-free and direct cell to cell routes. To differentiate infected donor cells from target cells, we labeled the donor cells with mCherry. We infected target cells in the absence of drugs or the presence of increasing concentrations of the anti-retroviral drugs tenofovir or efavirenz and calculated the ratio of the number of target cells infected with drug relative to the number of target cells infected without drug (F). We observed strikingly different responses to drugs when infection was initiated by donor cells relative to cell-free virus. When infection occurred solely with free virus, F showed a steep drop with increasing drug at the drug concentrations used. In contrast, when infection was mediated by an input of infected cells, F showed a more moderate slope of decrease. Values of F were about an order of magnitude larger for transmission from infected cells relative to infection by free virus at the highest drug concentrations tested. This can be understood using a simple probabilistic model which predicts that the average number of viruses transferred per direct cell to cell transmission is large. The decrease in infection observed for direct cell to cell infection at high drug concentrations was insufficient to stop the infection from propagating.

III. Conclusion

While the *in vivo* significance of these results has yet to be determined, the resistance of direct cell to cell infection to anti-retroviral therapy may indicate that this mode of infection may create a reservoir of ongoing replication in the presence of therapy levels that would sterilize infection by cell-free virus.

References

[1] A. S. Chuck, M. F. Clarke, B. O. Palsson (1996). Hum Gene Ther 7, 1527.
[2] R. Dulbecco, M. Vogt (1954) J Exp Med 99, 183.
[3] Q. Sattentau (2008). Nat Rev Microbiol 6, 815 (Nov, 2008).
[4] P. Chen, W. Hubner, M. A. Spinelli, B. K. Chen (2007) J Virol 81, 12582.
[5] W. Hubner et al. (2009). Science 323, 1743.
[6] D. Rudnicka et al.(2009). J Virol 83, 6234.
[7] S. Sowinski et al. (2008). Nat Cell Biol 10, 211.
[8] D. S. Dimitrov et al. (1993). J Virol 67, 2182.
[9] Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents (2008).

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