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Partial inhibition of HIV replication by type-I interferons: impact of cell-to-cell viral transfer

Daniela Vendrame, Marion Sourisseau, Virginie Perrin, Olivier Schwartz and Fabrizio Mammano*

Address: Institut Pasteur, Virus and Immunity Unit, CNRS URA 3015, 25-28 rue du Dr. Roux 75724 Paris, France
* Corresponding author

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Background

Type-I interferons (IFN) inhibit several steps of the human immunodeficiency virus type-1 (HIV) replication cycle. Some HIV proteins, like Vif and Vpu, directly counteract IFN-induced restriction factors. Other mechanisms are expected to modulate the extent of IFN inhibition. Here, we studied the impact of IFN on various aspects of HIV replication in primary T lymphocytes.

Methods

Primary T-lymphocytes were treated by different subtypes of IFN-a or by IFN-b (10 to 10000 IU/ml) before or after exposure to the virus. Infections were carried out with cell-free HIV particles (primary isolates and reference strains) and in an assay based on viral transfer through direct cell-to-cell contacts. We monitored over-time the amount of viral capsid (p24) protein in the culture supernatant and the appearance of newly infected cells in culture by intracellular Gag staining. In addition, we characterized viruses escaping the effect of IFN.

Results

When cells were pre-treated by IFN and infected by cell-free virus particles (reference strains), we confirmed the potent reduction of p24 production in the culture supernatants. In striking contrast, HIV spread, measured as the appearance of Gag-expressing cells in these cultures, was only transiently inhibited by IFN. Primary isolates displayed similar transient inhibition profiles. A Vpu-defective virus was also able to emerge in IFN-treated cultures, although less efficiently than its wild-type counterpart. The potency and the duration of IFN inhibition depended on virus input. Virus emergence was the consequence of suboptimal inhibition of HIV replication, and was not due to the selection of resistant variants. Post-infection treatment by IFN was largely ineffective at controlling virus spread. Cell-to-cell HIV transfer, a potent means of virus replication, was less sensitive to IFN than infection by cell-free virions, and likely represents a mechanism to escape IFN inhibition.

Conclusion

These results suggest that IFN are less active in cell cultures than initially thought. They help explain the incomplete protection by naturally secreted IFN during HIV infection and the unsatisfactory outcome of IFN-treatment in HIV-infected patients.