The retroviral transporter Rex hijacks the RNA helicase UPF1 in a CRM1 dependent manner.

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Background:
HTLV-1 or HIV-1 retroviruses evolved specific countermeasures to oppose the host antiviral arsenal. Here, we focused on the nonsense-mediated mRNA decay (NMD) recently described as such. NMD can regulate the expression of host mRNAs by active mRNA decay during translation. We and others also identified HTLV RNA among NMD substrates, what prompted us to decipher the different mechanisms implemented by HTLV to escape that threat and its consequences for the host.

Methods:
To address these questions, we choose a comparative approach between HTLV-1 and HIV-1, giving their similar use of the nuclear exportin CRM1.

Results:
Effectively, upon HTLV-1 and HIV-1 infection as well as Rex or Rev expression, we showed a common NMD inhibition, by measuring RNA decay. By immunoprecipitation approaches (co-IPs and RNA-IPs) and confocal microscopy in HTLV chronically infected cells as well as cells expressing Rex mutants, we were able to decipher this NMD inhibition at a functional and molecular level: on one side our experiments demonstrate a nuclear sequestration of the NMD helicase UPF1 by Rex in a CRM1-UPF1-Rex complex and on the other side we proved that Rex expression lead to a decrease in UPF1 affinity for cellular RNA (including NMD targets). Unexpectedly, we also found that UPF1 is still present on HTLV RNA supporting the idea of a selective loading of the UPF1 helicase during viral RNA export and a new role during the virus life cycle.

Conclusion:
We conclude that NMD inhibition by HTLV-1 Rex interferes with the CRM1-dependant nuclear export pathway favouring the hijacking of UPF1 on viral RNA. We suggest that this model may be shared by other viruses expressing Rev like proteins.

Disclosure of Interest Statement:
None.