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Oral presentation

The HIV-2 Vpx protein usurps the Cul4A-DDB1-DCAF1 ubiquitin ligase to overcome a post-entry block in macrophage infection

Diana Ayinde*[1,2], Anna Bergamaschi[3], Annie David[3], Erwann Le Rouzic[1,2], Marina Morel[1,2], Sebastien Nisole[1,2], Florence Margottin-Goguet[1,2], Gianfranco Pancino[3] and Catherine Transy[1,2]

Address: [1]Institut Cochin, Université Paris Descartes, CNRS (UMR 8104), France, [2]Inserm, U567, 27 rue du faubourg St Jacques 75014 Paris France and [3]Institut Pasteur, Unité de Régulation des Infections Rétrovirales, 25 rue du Dr Roux 75724 Paris Cedex 15, France

* Corresponding author

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HIV and SIV genomes encode several auxiliary proteins which have increasingly shown their importance in the virus-host relationship. One of these proteins, Vpx, is unique to the HIV-2/SIVsm lineage and is critical for viral replication in macrophages. The functional basis for this requirement as well as the Vpx mode of action have remained a mystery for quite some time.

We have previously shown that HIV-1 Vpr induces cell cycle arrest by recruiting the CUL4A-DDB1^{DCAF1} ubiquitin ligase. This presumably leads to the degradation of a host factor required for cell cycle progression into mitosis. Vpr and Vpx proteins are evolutionary related and show significant sequence similarity even though they are not functionally redundant. This prompted us to address whether Vpx, like Vpr, recruits the CUL4A-DDB1^{DCAF1} ubiquitin ligase and whether Vpx uses this functional property to enable efficient macrophage infection by HIV-2.

Confirming this hypothesis, our results show that DCAF1 is a critical host effector of Vpx in its ability to mediate infection and long-term replication of HIV-2 in human macrophages. WT Vpx associates with the DDB1 component of the CUL4A ubiquitin ligase through DCAF1 binding. In contrast the Q76R Vpx mutant is unable to bind DCAF1 and recruit DDB1. When placed in the HIV-2 provirus, Q76R Vpx severely diminished viral replication in macrophages.

Vpx is incorporated into newly formed virions, suggesting an early function in the next infection cycle. Accordingly, precluding Vpx present in the incoming virions from recruiting DCAF1 in target macrophages leads to a postentry block characterized by defective accumulation of HIV-2 reverse transcripts. In addition Vpx from SIVsm functionally complements Vpx-defective HIV-2 in a DCAF1-binding dependent manner.

Altogether, our data point to a mechanism in which Vpx diverts the DCAF1 ubiquitin ligase to inactivate an evolutionary conserved factor (RF: restriction factor), which restricts infection of macrophages by HIV-2 and closely related simian viruses (Figure 1). This function of Vpx challenges the previous idea that Vpx complements the lack of cellular factors necessary for viral replication in macrophages. Vpx therefore acts similarly to other HIV auxiliary proteins (Vif, Vpu, Nef) known to inactivate cellular factors in order to create an advantageous environment for the virus.