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HIV-1 VPR impairs cell growth through the inactivation of two genetically distinct host cell proteins

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The most widely recognized property of the HIV-1 Vpr auxiliary protein is its ability to arrest cell cycle progression at the G2 phase, which eventually triggers an apoptotic response. There is a long standing controversy as to whether Vpr might exhibit cytopathic activity independently of its G2 arrest property.

We developed a clonogenic assay based on the expression of wild-type and mutant versions of Vpr using an EBV-based episome carrying a hygromycin resistance selection marker. Expression of the wt Vpr protein abrogated the formation of hygromycin-resistant cell colonies, confirming that long-term expression of Vpr is lethal in dividing cells. We previously showed that Vpr promotes G2 arrest through the recruitment of the DCAF1 adaptor of the Cul4A ubiquitin ligase. Intriguingly, several HIV-1 Vpr mutants, which are devoid of G2 arrest properties but conserve DCAF1 binding, strongly reduced the formation of hygromycin-resistant cell colonies. Long term expression of these mutants induced G1 arrest and apoptosis. Thus Vpr expression can cause cell death independently of its G2 arrest activity.

Disruption of the DCAF1-binding function of Vpr restored efficiency of colony formation indicating that recruitment of DCAF1 is required for this second cytotoxic activity of Vpr. However, DCAF1 binding is not sufficient to confer cytopathicity since Vpx from HIV-2/SIVsm does not impair colony formation.

Altogether our data indicate that Vpr exhibits two dictinct cytotoxic activities in dividing cells, which both require the recruitment of DCAF1. Based on the current view of Vpr mechanism of action, i.e. hijacking of the host ubiquitination machinery, Vpr likely induces the proteasome-mediated degradation of two host proteins which are independently required for proper cell growth. This work was supported by grants from ANRS, Sidaction, Fondation de France and Mairie de Paris.