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Roles of Vpr and Vpx in modulating the virus-host cell relationship

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Abstract

The human and simian immunodeficiency viruses contain small open reading frames known as *vpr* and *vpx*. These genes encode proteins that are highly related both at the amino acid level and functionally, although key differences do exist. This review describes the main functions ascribed to Vpr and Vpx in the context of both viral replication and modulation of host cell biology.

1. Introduction

HIV-1 Vpr (short for viral protein, regulatory) is a small, 96-amino acid protein of about 14kDa. The name assigned to this protein originated from the observation that disruption of its open reading frame in HIV-1 resulted in a virus that replicated with a slower kinetics (Hattori et al., 1990; Ogawa et al., 1989; Wong-Staal, Chanda, and Ghrayeb, 1987). HIV-1 Vpr is a small, 96-amino acid (14 kDa) protein. Vpr is packaged in the virus particles via a direct interaction with the p6 subunit of the Gag precursor (reviewed in (Tungaturthi et al., 2003)). Vpr is also expressed *de novo* by the provirus, from a singly-spliced, late mRNA (Schwartz, Felber, and Pavlakis, 1991).

A multiplicity of effects and functions have been ascribed to Vpr. As a virion-bound protein, Vpr has been proposed to participate in the nuclear import of pre-integration complexes in macrophages and other non-dividing cells; and to enhance the fidelity of reverse transcription. As a late protein produced in the infected cell, Vpr induces cell cycle arrest in the G_2 phase, transactivation of the viral promoter, and ultimately apoptosis (reviewed in (Le Rouzic and Benichou, 2005; Planelles and Benichou, 2010)).

2. Structure of Vpr

The structure of Vpr consists of three bundled α-helices spanning residues 17-33, 38-50 and 55-77, respectively. Flanking the triple helix bundle are flexible, unstructured n- and c-terminal domains that are negatively and positively charged, respectively (Figure 1) (Morellet et al., 2003). The carboxy-terminus of Vpr contains six arginine residues between positions 73 and 96 (Figure 1). This domain shows similarity with those of arginine-rich protein transduction domains, and may explain the transducing properties of Vpr, including its ability to cross the lipid bilayers (Coeytaux et al., 2003;Kichler et al., 2000;Sherman et al., 2002). The third helix

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of Vpr is rich in leucine residues (Schuler et al., 1999), and one side of the helix presents a stretch of hydrophobic side chains that can form a leucine zipper-like motif (Schuler et al., 1999). This region is thought to mediate the formation of Vpr oligomers (Fritz et al., 2008;Mahalingam et al., 1997;Schuler et al., 1999;Wang et al., 1996) and the interaction with a ubiquitin ligase complex (see below).

3. Effects of Vpr on the cell cycle

The ability of Vpr to manipulate the cell cycle and, more specifically, to induce arrest at the G_2-to-M transition was first reported in 1995 (He et al., 1995; Jowett et al., 1995; Re et al., 1995; Rogel, Wu, and Emerman, 1995). About one year prior to those reports, Zhao and collaborators described the first cellular protein found in association with Vpr in co-precipitation experiments (Zhao, Mukherjee, and Narayan, 1994). This was a novel cellular protein of unknown function, and was named Vpr-binding protein (VprBP) (Zhao, Mukherjee, and Narayan, 1994). Initial studies did not link VprBP to the cell cycle effects of Vpr and it was only recently that a direct link was found (see below).

4. Vpr induces genotoxic stress

The effects of Vpr on the cell cycle resemble those of DNA damage. More specifically, the presence of hyper-phosphorylated Cdk1, and the ability of methylxanthines, such as caffeine, to relieve the cell cycle block, suggested that the underlying stimulus was DNA damage (Poon et al., 1997; Shostak et al., 1999).

Roshal *et al.* showed that Vpr induced G_2 arrest via activation of ataxia telangiectasia-mutated and Rad 3- related kinase, ATR (Roshal et al., 2003). ATR is a sensor for replication stress, a cellular condition that involves the stalling of replication forks. Replication stress be induced by deoxyribonucleotide depletion, topoisomerase inhibition or ultraviolet light-induced DNA damage (reviewed in (McGowan and Russell, 2004)). The ATR phosphorylation target that controls G_2 checkpoint activation is Chk1 (Figure 2) (Cimprich and Cortez, 2008). In agreement with this idea, Roshal *et al.* also showed that depletion of Chk1 or ATR relieved Vpr-induced G_2 arrest (Roshal et al., 2003).

It remains unclear whether the Vpr effect on the cell cycle is a primary function of Vpr or, alternatively, a consequence of an unknown function of Vpr. Nevertheless, recent observations with infected cells from HIV-1-infected individuals indicate that infected CD4+ lymphocytes, in vivo, display a DNA content that is consistent with that of cells in the G_2/M transition (Zimmerman et al., 2006).

5. Vpr manipulates a ubiquitin ligase complex

In 2006, several groups identified a family of proteins that were associated with the damaged DNA-specific binding protein 1 (DDB1), a Cullin 4 adaptor (Angers et al., 2006; He et al., 2006; Higa et al., 2006a; Jin et al., 2006). This novel family of proteins, which include VprBP, act as the substrate receptors in a Cullin 4- and DDB1-based ubiquitin ligase complex or E3 (Angers et al., 2006; He et al., 2006; Higa et al., 2006a; Jin et al., 2006). VprBP was, accordingly, renamed DDB1- and Cullin 4-associated factor (DCAF) -1. Shortly thereafter, it was shown that, through its interaction with VprBP/DCAF1, Vpr is capable of binding to a larger complex that includes Cul4A, DDB1, Rbx1/Roc1 and a ubiquitin conjugating enzyme or E2 (Belzile et al., 2007; DeHart et al., 2007; Hrecka et al., 2007; Le Rouzic et al., 2007; Schrofelbauer, Hakata, and Landau, 2007; Tan, Ehrlich, and Yu, 2007; Wen et al., 2007).

DDB1 links Cul4A to a number of possible substrate receptors, collectively referred to as DCAFs. The ubiquitination targets for several DCAFs have been identified. For example,

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CDT2 (DCAF2) recruits the origin of replication licensing factor, CDT1 (Higa et al., 2003; Hu et al., 2004) to prevent re-replication of DNA. The damaged DNA-binding 2/xeroderma pigmentosum complementation group E protein (DDB2/XPE) is another DCAF that interacts with DDB1-Cul4A to promote degradation of XPC (Sugasawa et al., 2005), and the histones 3 and 4 (Wang et al., 2006), as part of the response to DNA damage. Cul4A- and Cul4B-containing E3 ligases are also responsible for destruction of the cyclin-dependent kinase inhibitor, p27, and cyclin E, respectively (Higa et al., 2006b). Thus, the general roles of $Cul4A^{DDB1}$ E3 ligases involve genome stability, DNA replication and cell cycle checkpoint control. Merlin, a tumor suppressor protein, is the only target of DCAF1 found to date (Huang and Chen, 2008). *In vitro*, Merlin accumulates in serum-starved cells, and blocks proliferation. Merlin is then degraded in response to serum stimulation, and this relieves the block to cell proliferation (Huang and Chen, 2008).

Based on the above evidence, a model has emerged in which Vpr binds to a $Cul4A^{DDB1/DCAF1}$ E3 ligase, to trigger polyubiquitination and, presumably, degradation of an unknown cellular protein (represented as "T" for "target" in Figure 2), resulting in activation of the G_2 checkpoint (reviewed in (DeHart and Planelles, 2008)). Direct evidence for the polyubiquitination and degradation of the putative target is not available. However, Richard et al. recently reported that overexpression of the ubiquitin K48R mutant, which blocks formation of poly-ubiquitin chains with the K48 linkage, abrogated the induction of γH2A-X foci in Vpr-expressing cells (Belzile et al., 2010). Since K48-linked poly ubiquitin chains target proteins for proteasomal destruction, it is tempting to speculate that the ubiquitination target of Vpr is ultimately degraded.

This model predicts that Vpr would be using two different interfaces to bind to VprBP/DCAF1 and the putative target protein. The domain of Vpr that binds to DCAF1 was mapped to the leucine-rich (LR) motif 60-LIRILQQLL-68 within the third α-helix of HIV-$1_{89.6}$ Vpr (Zhao, Mukherjee, and Narayan, 1994). A Vpr mutant disrupting the DCAF1 interaction, Vpr(Q65R), was described by Le Rouzic *et al.* (Le Rouzic et al., 2007). Consistent with the idea that DCAF1-Vpr interaction is required for Vpr function, Vpr(Q65R) failed to induce G_2 arrest (Le Rouzic et al., 2007).

In contrast, truncation of the c-terminal 18 residues of Vpr [Vpr(1-78)] or replacement of arginine at position 80 by alanine, Vpr(R80A), resulted in mutants with unaltered binding to DCAF1, but unable to induce G_2 arrest (DeHart et al., 2007; Le Rouzic et al., 2007). In addition, co-expression of either Vpr(1-78) or Vpr(R80A) (Figure 1) with wild-type Vpr resulted in a dominant-negative effect by either of the previous mutants (DeHart et al., 2007; Le Rouzic et al., 2007).

Together, the above observations indicate that (a) binding of Vpr to DCAF1 is necessary, but not sufficient, for induction of G_2 arrest; and (b) the carboxy-terminal domain of Vpr is likely required for the recruitment of a cellular protein, whose ubiquitination leads to G_2 arrest (Figure 2).

Vpr-induced G_2 arrest has two known downstream effects that likely contribute to the pathogenesis of HIV-1. First, the transcriptional activity of the viral promoter is increased by several fold during G_2/M (Goh et al., 1998; Hrimech et al., 1999; Zhu et al., 2001), leading to enhanced production of viral particles (Goh et al., 1998). Secondly, G_2 arrest leads to the commitment of infected cells to death by apoptosis (see below).

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6. Vpr is a potent pro-apoptotic protein

Vpr was found to be a potent inducer of cell death both when expressed alone or in the context of HIV-1. Vpr-induced cell death has the hallmarks of apoptosis (Andersen et al., 2005; Muthumani et al., 2002; Shostak et al., 1999; Stewart et al., 2000).

Recombinant Vpr was found to associate with purified mitochondria (Jacotot et al., 2000; Vieira et al., 2000). This interaction was mediated via binding to the adenine nucleotide transporter (ANT), a component of the permeability transition pore (PTPC) that resides at the inner mitochondrial membrane (Jacotot et al., 2000; Vieira et al., 2000). The addition of recombinant Vpr to purified mitochondria triggered mitochondrial membrane permeabilization and release of pro-apoptotic proteins, such as cytochrome c (Jacotot et al., 2000; Vieira et al., 2000).

Recent studies of ANT and cyclophilin D (an essential regulatory element of ANT (Tsujimoto and Shimizu, 2007)) in knockout mice suggest that these mitochondrial pore components may promote necrotic, but not apoptotic cell death (Baines et al., 2005; Kokoszka et al., 2004; Nakagawa et al., 2005). In recent studies, siRNA-mediated depletion of ANT did not affect Vpr-induced apoptosis, whereas depletion of another mitochondrial pore-forming protein, Bax (Figure 2), effectively blocked apoptosis (Andersen et al., 2006).

An alternative explanation for Vpr-induced cell death is that apoptosis represents a downstream consequence of prolonged G_2 arrest (Andersen et al., 2006; Jacquot et al., 2007; Yuan, Xie, and Chen, 2003). Specifically, the pro-apoptotic activity of Vpr was eliminated when cells were artificially synchronized at the G_1/S boundary and therefore not allowed to progress into G_2 (Andersen et al., 2006). Furthermore, G_2 arrest and apoptosis induction by Vpr are dependent on the activation of ATR, and phosphorylation of its target, BRCA1 (Andersen et al., 2006). BRCA1 phosphorylation leads to GADD45α upregulation and induction of apoptosis (Andersen et al., 2006) (Figure 2). The signaling events that connect GADD45α and Bax are not known.

Tissue macrophages infected with HIV-1 are relatively resistant to the viral cytopathic effects (Gartner et al., 1986; Gorry et al., 2005; Kedzierska and Crowe, 2002). Thus, macrophages are considered one of the reservoirs for HIV-1 infection, and are capable of disseminating the virus to various tissues including the brain (Ghorpade et al., 1998; Orenstein, Fox, and Wahl, 1997). We have observed that macrophages are refractory to Vpr-induced apoptosis (Zimmerman et al., 2006). Western blot demonstrated the absence of three essential proteins in the ATR signaling axis: ATR itself, Chk1 and Rad17 (Zimmerman et al., 2006). In view of these results, we have speculated that the apparent lack of Vpr-induced cytopathicity in macrophages may due to the absence of ATR signaling (Zimmerman et al., 2006).

7. Vpr modulates the expression of natural killer cell ligands

Activation of the DNA damage pathway proteins ATR and ATM, after cells were exposed to genotoxic stress, resulted in the expression of ligands for the NK cell activation receptor, natural killer group 2, member D (NKG2D) (Gasser et al., 2005; Guerra et al., 2008). While the observations by Gasser et al. were obtained in the areas of cancer and genomic stability (Gasser et al., 2005), they opened the possibility that a virus that is capable of inflicting genotoxic stress may also induce NKG2D ligands. Specifically, two different teams tested whether Vpr-mediated activation of ATR may trigger upregulation of NKG2D ligands (Richard et al., 2009; Ward et al., 2009).

NKG2D is a single pass type II transmembrane protein consiting of 216 amino acid residues (Houchins et al., 1991). This receptor exists on the cell surface as a homodimer that contains

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a single C-lectin domain on each chain. NKG2D is part of an oligomeric complex with the transducing polypeptide DAP10 (Wu et al., 1999). DAP10 is a signaling adaptor protein that contains a cytoplasmic YINM motif that allows the recruitment and subsequent activation of phosphatidyl inositol 3-kinase (Wu et al., 1999). NKG2D is expressed on virtually all NK cells in the blood and on subsets of activated CD8+ T cells, γδ T cells and NKT cells (Bauer et al., 1999).

The ligands for NKG2D are are evolutionarily related to MHC class I molecules, although with clear functional differences. Unlike MHC I molecules, NKG2D ligands are devoid of CD8 binding, do not load peptides, and fail to associate with β2-microglobulin (Bahram et al., 1994; Groh et al., 1998). The human ligands for NKG2D include the transmembrane proteins, MHC class I polypeptide-related sequence-A (MICA) and –B (MICB) (Bahram et al., 1994) and the GPI-linked proteins, cytomegalovirus unique long 16 (UL16)-binding protein (ULBP) 1-4 (Cosman et al., 2001).

NKG2D ligands are expressed on certain tumor cell lines and in fetal tissues. Normal adult tissues may express these ligands but at much lower levels than those found on cell lines (Cosman et al., 2001). NKG2D ligands are induced on normal adult tissues after infection by certain viruses (Jonjic, Polic, and Krmpotic, 2008). Binding of NKG2D ligands to NKG2D on NK cells triggers a cytotoxic response as well as the release of multiple cytokines and chemokines (Kubin et al., 2001; Pende et al., 2002). Because NKG2D ligation elicits strong NK responses, viruses have developed strategies to down modulate NKG2D ligands on the infected cell surface. For example, human cytomegalovirus, which induces the expression of NKG2D ligands on infected cells, also encodes UL16 and UL142 that, in turn, cause intracellular sequestration of the same ligands, resulting in inhibition of their function (Cosman et al., 2001; Kubin et al., 2001).

HIV-1-infection of primary CD4+ T-cells leads to the induction of NKG2D ligand surface expression (Cerboni et al., 2007; Ward et al., 2007). These molecules were not only found on in vitro-infected primary CD4+ T-cell blasts but also on infected cells obtained from HIV-1-infected patients after amplification of the virus-infected cells ex vivo (Fogli et al., 2008). In addition, these studies, which used primary CD4+ T-cells infected with HIV-1 as targets for autologous NK cells in cytotoxicity assays, revealed that NK cells can respond to the HIV-1-infected cells in an NKG2D-dependent manner (Fogli et al., 2008; Ward et al., 2007; Ward et al., 2009).

Recent studies have shown that expression of the HIV-1 Vpr protein is sufficient for induction of expression of NKG2D ligands on the cell surface and that this action was mediated solely through ATR (Richard et al., 2009; Ward et al., 2009). HIV-1 Vpr, however, only upregulates the expression of ULBP-1 and -2 but not that of ULBP-3, MICA and MICB in primary CD4 + T-cells (Ward et al., 2009). The upregulation of ULBP-1 and -2 proteins on the cell surface was accompanied by increased mRNA levels for ULBP-1 and -2 (Ward et al., 2009). The presence of ULBP-1 and ULBP-2 on HIV-1 infected cells is dependent on the ability of Vpr to associate with the Cul4A$^{DDB1/DCAF1}$ ubiquitin ligase (Richard et al., 2009; Ward et al., 2009). Thus, the Vpr mutation, Q65R, which disabled binding of Vpr to DCAF-1, or knockdown of DCAF-1, abolished the Vpr effect on ULBP-1 and -2 (Ward et al., 2009).

To determine whether the expression of ULBP-1 and -2 could trigger NK cell killing of infected T-cells, NK cells were co-cultured with target cells infected with wild-type or Vpr-deleted HIV-1. NK cells, when exposed to T-cells infected with a Vpr-deficient virus, were two-fold less as efficient at lysing infected cells than when exposed to T-cells infected with a wild-type virus (Ward et al., 2009). Moreover, blocking the NKG2D receptor on NK cells diminished the lysis of T-cells infected with virus containing Vpr (Ward et al., 2009).

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In studies by Cerboni et al., HIV-1 Nef had been implicated in down-modulation of the NKG2D ligands, MICA, ULBP-1 and -2 on CD4+ Jurkat cell lines (Cerboni et al., 2007). However, in our recent studies we observed that deletion of Nef did not affect expression of these ligands on primary CD4+ T-cells (Ward et al., 2009). The reasons for this discrepancy are not known.

Efficient lysis by NK cells requires the recognition of NKG2D ligands in combination with co-activation receptors, such as 2B4 or NTB-A (Bryceson, Ljunggren, and Long, 2009; Bryceson et al., 2005; Bryceson et al., 2006a; Bryceson et al., 2006b). The previous idea is consistent with the observation that HIV-1 down modulates the ligands of 2B4 and NTB-A (CD48 and NTB-A, respectively) on infected cells (Ward et al., 2007). Therefore, we speculate that the modest killing effect that was observed in the presence of ULBP-1 and -2 downregulation (Ward et al., 2009) would be enhanced if simultaneous downregulation of 2B4 and/or NTB-A were abrogated. This remains to be tested.

8. Vpx as a paralog of Vpr

Viruses in the HIV-2/SIVsm/SIVmac lineage encode two proteins that are homologous to HIV-1 Vpr, namely Vpr and Vpx. While HIV-2 Vpr shares the ability to induce G_2 arrest with HIV-1 Vpr (Fletcher et al., 1996; Planelles et al., 1996), HIV-2 Vpx has no effect on the cell cycle and, instead, is required for efficient infection of non-dividing cells such as macrophages and dendritic cells (Fletcher et al., 1996; Guyader et al., 1989; Pancio, Vander Heyden, and Ratner, 2000; Yu et al., 1991). *Vpx* is thought to have arisen via a duplication of *vpr* within the HIV-2/SIVsm/SIVmac group (Sharp et al., 1996; Tristem et al., 1992), which diverged from the other primate lentiviral groups (Tristem et al., 1992). Given the common evolutionary origin, the high degree of homology, and the divergent functions of Vpx with respect to HIV-1 Vpr, Vpx is considered a paralog of HIV-1 Vpr.

Vpx facilitates the nuclear import of pre-integration complexes and/or promotes the accumulation of full-length viral DNA in non-dividing cells (Fletcher et al., 1996; Fujita et al., 2008; Goujon et al., 2007; Sharova et al., 2008; Srivastava et al., 2008). To explain the ability of Vpx to enhance lentiviral infection of dentritic cells, it has been proposed that Vpx overcomes an unknown restriction factor (Goujon et al., 2007). It has also been proposed that the restriction mechanism involves the ubiquitin/proteasome system, since treatment with proteasome inhibitors has a similar effect to that of Vpx expression (Goujon et al., 2007). Restriction factors are typically genetically dominant. In agreement with that, when Sharova *et al.* fused permissive cells (infection of which does not require Vpx) with restricting ones, the resulting heterokaryons had the restricting phenotype (Sharova et al., 2008).

The finding that HIV-1 Vpr manipulates the $Cul4A^{DDB1/DCAF1}$ ubiquitin ligase prompted studies to examine the interaction of Vpr and Vpx alleles from other primate lentiviruses with DCAF1. It was shown that SIV_{MAC} and HIV-2 Vpr interacted with DCAF1 (Le Rouzic et al., 2007; Wen et al., 2007). Le Rouzic *et al.* found that the SIVmac Vpx, which has no apparent effect on the cell cycle, also binds to DCAF1 (Le Rouzic et al., 2007). Binding of lentiviral Vpr and Vpx proteins to DCAF1 is mediated by a highly conserved leucine-rich motif (Le Rouzic et al., 2007). It is tempting, then, to speculate that Vpr and Vpx have preserved through evolution the ability to recruit DCAF1, although for different purposes.

Two recent reports demonstrated that the interaction of Vpx with DCAF1 is required for the enhancement of infectivity of non-dividing cells (Sharova et al., 2008; Srivastava et al., 2008). These studies show that depletion of DCAF1 via RNA interference (Sharova et al., 2008; Srivastava et al., 2008) or expression of a Vpx mutant, Q76A, devoid of DCAF1 binding (Srivastava et al., 2008) ablated the enhancement of infectivity by Vpx.

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Unlike lentiviruses, gammaretroviruses, such as the murine leukemia virus (MLV) are unable to infect non-dividing cells. Examples of physiologically relevant non-dividing cells include monocytes, monocyte-derived macrophages (MDM), microglial cells and dendritic cells. In the laboratory, non-dividing cells can artificially be generated by treatment of immortalized cell lines with certain chemicals, such as aphidicolin, an inhibitor of DNA polymerases. Kaushik et al. recently demonstrated that the restriction in primary cell types is of a different nature from that observed in artificially arrested cell lines (Kaushik et al., 2009). While the block to MLV replication in macrophages is at or prior to the step of reverse transcription, this is not the case in arrested HeLa cells, where reverse transcription proceeds similarly to that in dividing cells (Kaushik et al., 2009). Kaushik et al. also showed that the ability of Vpx to overcome a putative restriction to SIV and HIV-1 in non-dividing primary cells was also active in overcoming the restriction to MLV in such cell types. The ability of Vpx to overcome the block to MLV infection was shown by preinfection with viruses encoding Vpx, but also by constructing a chimeric MLV Gag protein encoding SIV p6. SIV p6 is binds to Vpx and mediates Vpx encapsidation in virus particles. This p6-chimeric MLV acquired the ability to infect macrophages, but only when it was produced in the presence of Vpx (Kaushik et al., 2009).

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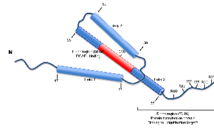

Figure 1.
Diagramatic structure of Vpr as determined by nuclear magnetic resonance (adapted from Morellet et al., 2003). Cilinders denote regions of alpha helix comprised between residues indicated by numbers. N, amino-terminus. C, carboxy-terminus.

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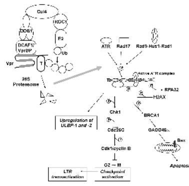

Figure 2.

Signaling pathways proposed to mediate induction of G_2 arrest, ULBP-1 and -2 expression, apoptosis, and LTR transactivation by HIV-1 Vpr. Ub, ubiquitin.

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