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Review

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.

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1. Introduction

HIV-1 Vpr (short for viral protein, regulatory) is a small, 96-amino acid protein of about 14 kDa. 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 et al., 1987). Vpr is packaged in 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 et al., 1991).

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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 (Fig. 1) (Morellet et al., 2003). The carboxy-terminus of Vpr contains six arginine residues between positions 73 and 96 (Fig. 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 lipid bilayers (Coeytaux et al., 2003; Kichler et al., 2000; Sherman et al., 2002). The third helix 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 et al., 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 et al., 1994). This was a novel cellular protein of unknown function, and was named Vpr-binding protein (VprBP) (Zhao et al., 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).

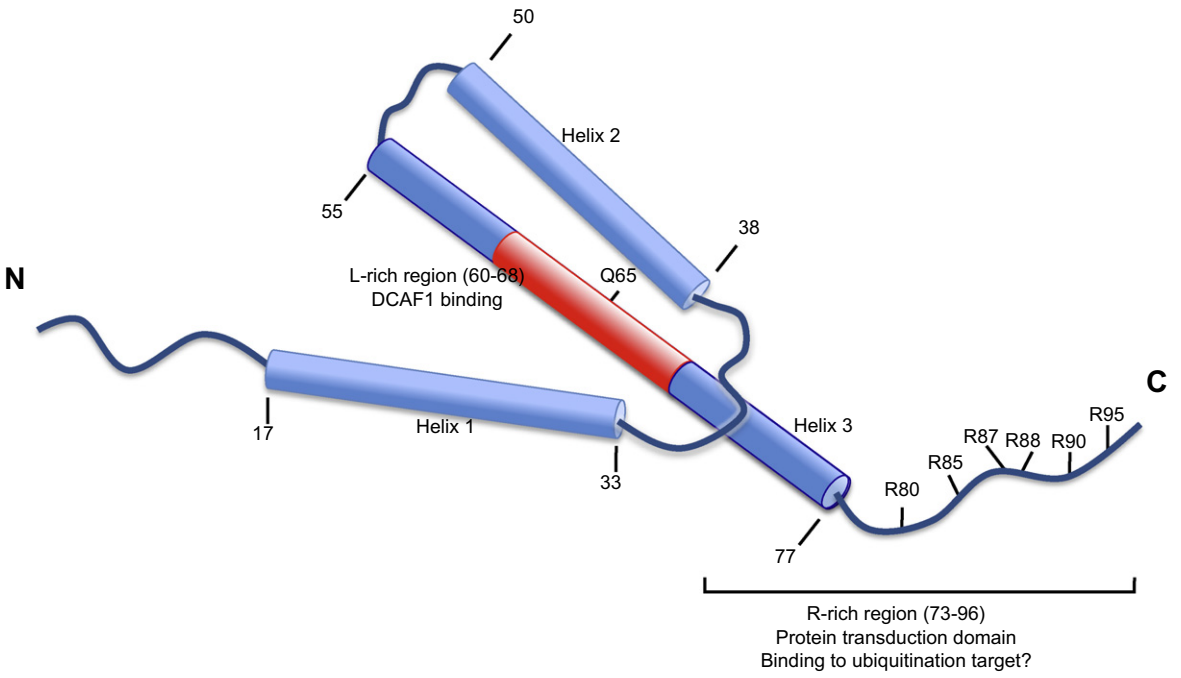

Fig. 1. Diagramatic structure of Vpr as determined by nuclear magnetic resonance (adapted from Morellet et al., 2003). Cylinders denote regions of alpha helix comprised between residues indicated by numbers. N, amino-terminus. C, carboxy-terminus.

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