

Review

Role of Viral Protein U (Vpu) in HIV-1 Infection and Pathogenesis

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Abstract: Human immunodeficiency virus (HIV)-1 and HIV-2 originated from cross-species transmission of simian immunodeficiency viruses (SIVs). Most of these transfers resulted in limited spread of these viruses to humans. However, one transmission event involving SIVcpz from chimpanzees gave rise to group M HIV-1, with M being the principal strain of HIV-1 responsible for the AIDS pandemic. Vpu is an HIV-1 accessory protein generated from *Env/Vpu* encoded bicistronic mRNA and localized in cytosolic and membrane regions of cells capable of being infected by HIV-1 and that regulate HIV-1 infection and transmission by downregulating BST-2, CD4 proteins levels, and immune evasion. This review will focus of critical aspects of Vpu including its zoonosis, the adaptive hurdles to cross-species transmission, and future perspectives and broad implications of Vpu in HIV-1 infection and dissemination.

Keywords: human immunodeficiency virus-1 and -2; simian immunodeficiency viruses; viral protein U (Vpu); bone marrow stromal antigen 2; transmembrane domain; endoplasmic reticulum-associated degradation pathway; endosomal sorting complexes required for transport; endolysosomes; autophagy



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1. Introduction

Human immunodeficiency virus (HIV) is a lentivirus that belongs to the Retroviridae family. The HIV retrovirus contains two RNA molecules with three prototypic genes that encode group-specific antigen (*gag*), envelope (*env*), and polymerase (*pol*) proteins [1–3]. HIV isolates have been classified into two types: HIV-type 1 (HIV-1) and HIV-type 2 (HIV-2). HIV-1 is the causative agent of HIV/AIDS, while HIV-2 is constrained to some well-defined Central and Western Africa regions; relative to HIV-1, HIV-2 has weak transmission capabilities [4,5]. Based on phylogenetic analysis, HIV-1 shows substantial similarities to the virus SIVgor that infects gorillas (*Gorilla gorilla*) and the virus SIVcpz that infects chimpanzees (*Pan troglodytes troglodytes*). HIV-2 resembles the virus SIVsmm that infects sooty mangabey monkeys (*Cercocebus atys*). HIV-1 evolved from chimpanzees and/or gorillas by independent cross-species transmissions of SIVs [4,5].

The HIV-1 virus has been subdivided into M, N, O, and P subtypes according to their origin and distribution patterns within the human population. HIV-1 M is globally distributed and is a major factor causing the pandemic disease AIDS. HIV-1 N is rare (non-major/non-outlier) and originated from chimpanzees [5]. HIV-1 O and P groups have close relationships to the virus SIVgor isolated from gorillas; geographically, the O group virus is constrained to Cameroon and surrounding countries [5]. The P group virus was discovered to come from two individuals in Cameroon. Vpu protein is encoded by all groups of HIV-1, but biological differences have been noted between the various sources of Vpu proteins. Pandemic M group viruses contain Vpu proteins that are more highly active than do other groups [5]. Clearly, one needs to understand the functions of Vpu proteins to understand their roles in controlling HIV-1 infection and HIV/AIDS disease pathogenesis.

2. Vpu Gene and Its Diversification

Vpu was initially characterized as an U open reading frame (ORF) product localized in the HIV-1 genome between the *env* and *tat* exons [6]. The Vpu protein is translated from bicistronic mRNA of *env-vpu* presumably through leaky scanning of ribosomes from the initiation codon of the *vpu* gene [7,8]. The *vpu* gene is encoded in the HIV-1 genome, but it is not present in the genomes of HIV-2 and of SIVs such as SIV from rhesus macaques (SIVmac) and SIV from sooty mangabey (SIVsmm) [4,5,9]. However, structural homologs of Vpu have been identified in SIV from chimpanzee (SIVcpz), as well as in SIV from the greater spot-nosed monkey (*Cercopithecus nictitans*; SIVgsn), the mona monkey (*Cercopithecus mona*; SIVmon), the mustached monkey (*Cercopithecus Cephus*; SIVmus), Dent's mona monkey (*Cercopithecus mona denti*; SIVdent), and recently in gorilla (*Gorilla gorilla*; SIVgor) [9–13].

3. Vpu Protein and Its Cellular Distribution

Vpu is a multimeric integral membrane phosphoprotein with 81 amino acids [14,15]. It has three distinct alpha-helices: the N-terminus proximal transmembrane domain (Helix1-TMD: 6–29 residues) and two C-terminus domains, Helix 2 (32–52 residues) and Helix 3 (57–72 residues) [16–19] (Figure 1). Helix-2 is amphipathic and is hydrophobic with polar residues on the sides. The hydrophobic portion is buried in plasma membranes, while the hydrophilic region is cytoplasmic [20]. Helix-3 contains acidic amino acids interconnected by two phosphorylated Serine residues: S52 and S56 [21]. Protein kinase casein kinase 2 (CK-2) catalyzes the phosphorylation of the serines (Figure 1) and these post-translational modifications regulate associations between Helix 3 and beta-TrCP/ubiquitin ligase complexes [22,23]. Vpu once oligomerized can form pentameric pore-like structures through which selective monovalent cations can pass [24–26].

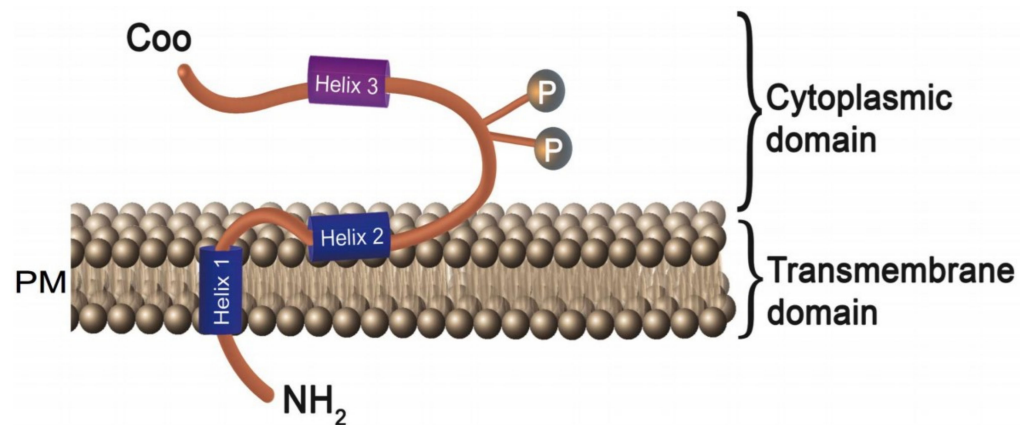


Figure 1. Structure of the human immunodeficiency virus (HIV)-1 accessory protein Vpu. Vpu protein is composed of three different distinct alpha helices: the N-terminus proximal transmembrane domain (Helix1-TMD: 6–29 residues) and a cytoplasmic domain that consists of two alpha helices (Helix 2: 32–52 residues, Helix 3: 57–72 residues). The first cytoplasmic helix shows amphipathic behavior with hydrophobic and polar residues on the sides. The hydrophobic portion is buried in the cell membrane, while the hydrophilic region is exposed to the cytoplasmic side. The second cytoplasmic helix is formed by acidic amino acids. Two phosphorylated serine residues, S52 and S56, interconnect these cytoplasmic helices.

Vpu proteins localize to the plasma membranes, endoplasmic reticulum (ER), and trans-Golgi network (TGN) [27–30]. Sequence analysis of the cytosolic domain of Vpu shows the presence of putative trafficking signals that carry variations in amino acid residues among different subtypes of Vpu. These signals include YXXΦ, a conserved tyrosine-based sorting motif (where Φ represents a hydrophobic residue), and a ([D/E]XXXL [I/V]) sorting motif consisting of acidic residue/dileucine-based sequences that

are present in the hinge portion between the cytosolic domain and the TMD. The latter is involved in endocytosis and the targeting of transmembrane host proteins to lysosomes [31]. Another ([D/E] XXXL [/I/V]) motif is present in the second alpha-helix of the cytoplasmic domain [29]. Several primary isolates of HIV-1 and laboratory-adapted viruses carry polymorphisms of the *vpu* gene that are based on variations of putative trafficking signal sequences [32] and these polymorphisms regulate subcellular distribution patterns and biological activities of the Vpu protein.

4. Role of Vpu Protein in HIV-1 Pathogenesis

Vpu has two well-established functions in HIV-1 infection. First, through the ubiquitin-proteasomal pathway, it enhances the degradation of CD4 protein produced *de novo* in the endoplasmic reticulum [33]. Second, Vpu augments the release of progeny virions from infected cells [23,34,35] by counteracting the effect of Tetherin, a host restriction factor. Tetherin, also known as BST-2, CD317, or HM1.24, strongly inhibits the release of virions from infected host cells [28,36,37]. In addition, Vpu also regulates the transport of host proteins from ER to Golgi [38], modulates MHC class II presentation [39], induces the stabilization of p53 [40], induces degranulation of natural killer cells (NK cells) by NTB-A downmodulation, inhibits lipid antigen presentation through CD1d downmodulation [41,42], induces apoptosis, and impairs migration and chemotactic signaling within CD4⁺ T-cells through CCR7 downregulation [43].

4.1. Role of Vpu in HIV-1-Induced CD4 Receptor Downregulation

CD4 is the primary receptor through which primate lentiviruses enter target cells [44]. It is a 54 kDa type-I integral glycoprotein expressed on the surface of cells including helper T-lymphocytes, monocyte/macrophage lineage cells, and hematopoietic progenitor cells. HIV-1 infection of these cells leads to a reduction in the cell surface levels of CD4 receptors [45]. CD4 downregulation has been proposed to block the superinfection of target cells [46] and protect the infected cell from host immune responses, and favors viral replication fitness [47] (Table 1). Constitutive expression of CD4 can be harmful to productive viral replication and dissemination [48]. *De novo* produced CD4 molecules bind Env polyproteins with high affinity within the endoplasmic reticulum, prevent the transport and processing of Env precursor to its products gp41 and gp120 [49,50], and reduce secretion of infectious progeny virion particles from infected cells.

Table 1. Function of Vpu proteins of different HIV-1 groups.

Vpu functions	Functions of Diverse Vpu Proteins			
	HIV-1 M	HIV-1 N	HIV-1 O	HIV-1 P
BST-2 downregulation [4,5,9,51–53]	Y	Y	N	N
CD4 degradation [4,5,9,51,52]	Y	N	Y	Y
NTB-A downmodulation [54,55]	Y	N	UN	UN
CD1d downmodulation [42,55,56]	Y	N	Y	Y
CCR7 downmodulation [43]	Y	UN	UN	UN

Abbreviations: Y: yes, N: no, UN: unknown, BST-2: bone marrow stromal antigen-2, NTB-A: natural killer T- and B-cell antigen, CD1d: cluster differentiation 1d, CCR7: CC-chemokine receptor-7, HIV-1 M: HIV-1 major, HIV-1 N: HIV-1 non-outlier, HIV-1 O: HIV-1 outlier, HIV-1 P: HIV-1 putative.

Vpu can enhance degradation of *de novo* produced CD4 by retention of CD4 in the endoplasmic reticulum through interactions between Vpu and CD4 via their transmembrane domains, poly-ubiquitination of CD4, and transport to the ERAD (ER-associated degradation) pathway [33,57,58]. The integrity of the cytoplasmic domain of Vpu protein

and the DSGXXS motif containing the S52/S56 phosphoserine residues are critical to proteasomal degradation of CD4; Vpu interacts directly with β -TrCP1, β -TrCP2 (β -transducin repeat-containing protein 1 or 2), two adaptor molecules (SKP1-cullin-F-Box), and the E3 ubiquitin ligase complex [59,60]. The interaction of SCF- β -TrCP with Vpu induces the poly-ubiquitination of CD4 through binding to lysine, serine, and threonine residues [58] (Figure 2). Without those residues, SCF-mediated interactions between Vpu with CD4 result in retention of the receptor in the ER. Without the ERAD complex (VCP-UFDL1-NPL4), Vpu fails to pull CD4 out of the endoplasmic reticulum and reduces proteasomal degradation [58] (Figure 2). Decreased interactions between β -TrCP/Vpu reduce proteasomal degradation by the ERAD pathway of several cellular factors including β -catenin, ATF4, and p53 [40].

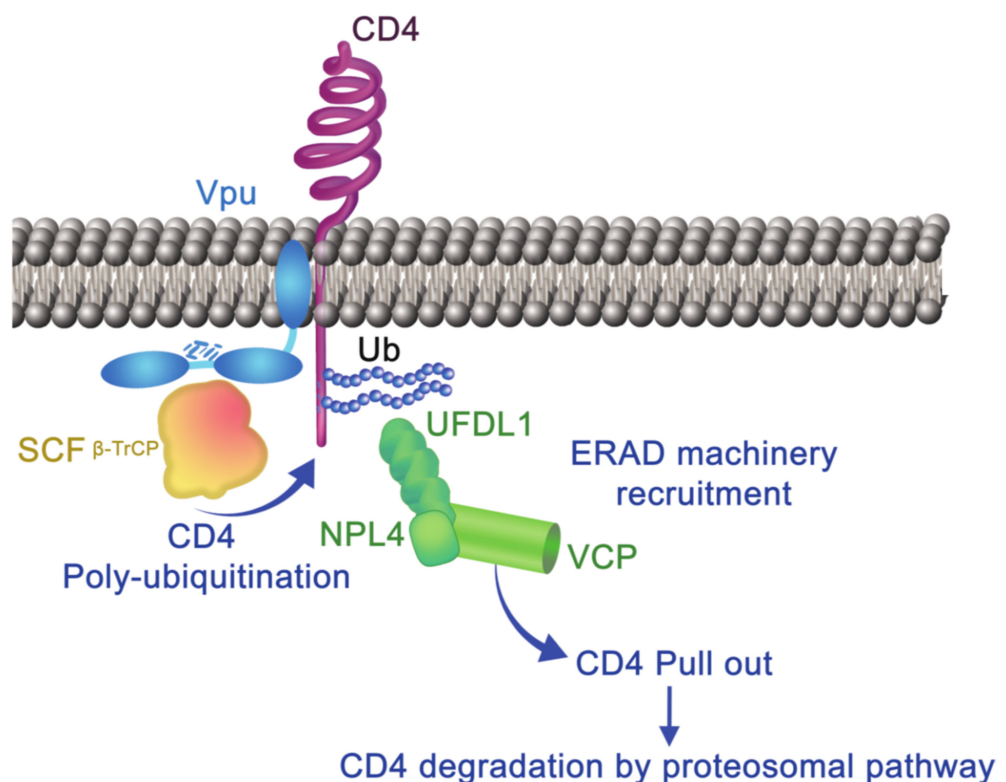


Figure 2. Endoplasmic reticulum-associated degradation of CD4 by Vpu protein: Vpu interacts with CD4 by transmembrane–transmembrane domain in the ER and promotes binding with SKP1-cullin1-F-Box (SCF) E3 ubiquitin ligase through the SCF subunits β -TrCP1 and β -TrCP2. Vpu and SCF β -TrCP complex induces proteasomal degradation of CD4 by the ERAD pathway by extracting it from ER. Abbreviations: Vpu: viral protein U, CD4: cluster differentiation 4, Ub: ubiquitination, SCF β -TrCP: SKP1-cullin1-F-Box- β -transducin repeat-containing proteins, UFDL1: ubiquitin fusion degradation 1-like, NPL4: nuclear protein localization protein 4, ERAD: endoplasmic reticulum-associated degradation, VCP: valosin-containing protein.

4.2. Role of Vpu in BST-2 Downregulation and Virus Release

Vpu increases the release of HIV-1 from HIV-1-infected cells [15,34]. As confirmed by electron microscopy (EM), Vpu defective virion particles accumulate at the budding site on infected host cell membranes [35,61]. The role of Vpu in virus release varies between cell types. For example, the release of Vpu-defective HIV-1 particles was strongly reduced in HeLa cells, but it was not affected in COS, HEK293T, CV-1, and Vero cells [62–64]. The BST-2 protein was identified as a restriction factor that blocked the release of mutant viruses lacking the accessory gene *vpu* [28,36] that is constitutively expressed in HeLa cells, but not in permissive cell lines like HT1080 and HEK293T. The expression of BST-2 and its restrictive phenotype could only be maintained by IFN- α/β induction in permissive

cells and increased in Jurkat and primary CD4⁺ T-cells. Moreover, the induction of BST-2 expression in HT1080 and HEK293T cells restricted the secretion of virus particles in the absence of Vpu protein [28,36] and siRNA-mediated reduction of BST-2 expression in HeLa cells led to the efficient release of Vpu defective virion particles [28,36].

BST-2 can inhibit the release of almost all enveloped viruses, including retroviruses, flaviviruses, herpesviruses, arenaviruses, rhabdoviruses, and paramyxoviruses [65,66]. Therefore, BST-2 has been proven to be a critical innate immune factor for restricting viral release. Primate lentiviruses express three different proteins that counteract BST-2 antiviral activity: Vpu for HIV-1 [28,36]; Nef for SIV major isolates [51,67,68]; and Env for HIV-2, SIVagmTan, and SIVmac239 Δ nef isolates [69–72]. HIV-1 Vpu, HIV-2 Env, and SIV Nef all decrease cell surface levels of BST-2 from budding viral sites to favor virus release [69–72].

BST-2 is a 30–36 kDa type II integral membrane protein that is expressed constitutively as well as following induction by type-I interferon or other pro-inflammatory signals [65]. It consists of a short N-terminal cytoplasmic tail inter-linked to a transmembrane domain and an extracellular domain anchored in the membrane via its glycosylphosphatidylinositol (GPI) moiety in the C-terminal region [73]. BST-2 is distributed mainly in cholesterol-rich microdomains of the cell membrane and intracellular compartments such as the trans-Golgi-network (TGN) and endosomes [73,74].

BST-2 can physically tether de novo generated virion particles at the cell membrane of infected cells, thereby decreasing virus release [75,76]. This tethering occurs following formation of homodimers via parallel disulfide-bonding and cross-linking with virions particles and plasma membranes through its membrane anchoring N-terminal domains [75,77]. BST-2 makes “axial” arrangements in which the BST-2 GPI anchors remain connected to the membrane of infected cells. Vpu downregulates BST-2 and interactions between Vpu and BST-2 utilize their respective transmembrane domains. The Ala14, Ala18, and Trp22 residues of the Vpu TMD are crucial for BST-2 downregulation from the cell membrane through direct interaction with specific residues on BST-2 (Val, Iso, Leu, and Leu) [78,79]. These residues are involved in TMD–TMD interactions, create an anti-parallel helix–helix interface [80], and maintain the interaction between these proteins [81,82]. The antagonistic effect of Vpu on BST-2 activity takes place by three sequential steps: downregulation from the cell surface, restriction of BST-2 recycling, and decline in intracellular BST-2 levels. Downregulation of BST-2 at the cell surface is mediated by clathrin-coated vesicles through direct interaction of the AP2 (clathrin adaptor complex) with a Y6XY8 motif (non-canonical dual Tyrosine residues) present in the cytoplasmic tail of BST-2 [74,83]. Vpu restricts the recycling of internalized BST-2 to the cell membrane and blocks the translocation of de novo generated BST-2 to the cell membrane [84–87].

BST-2 is degraded by ubiquitination following recruitment of the SCF- β -TrCP-E3 ligase complex to the DS52GxxS56 motif that is present in the cytosolic region of Vpu [88,89] (Figure 3). Vpu enhances ubiquitination of BST-2 through lysine/serine and threonine amino acid residues present in the cytoplasmic tail of Vpu [89]. Vpu induces ubiquitination and degradation of both BST-2 and CD4 by identical molecular mechanisms, although the outcomes are different. Instead of targeting BST-2 to proteasomes, Vpu induces the β -TrCP-dependent sorting of BST-2 to lysosomes [77,84,88]. Moreover, it has been shown that the ESCRT complex and Rab7 are critical components of the endo-lysosomal trafficking involved in the degradation of BST-2 [90,91] (Figure 3).

Of the four HIV-1 groups, the M group is the most highly pathogenic and transmissible because Vpu is highly active, and this increases the ability of the virus to disseminate from one cell to another by counteracting the host protein BST-2 and evading the immune system (Table 1).

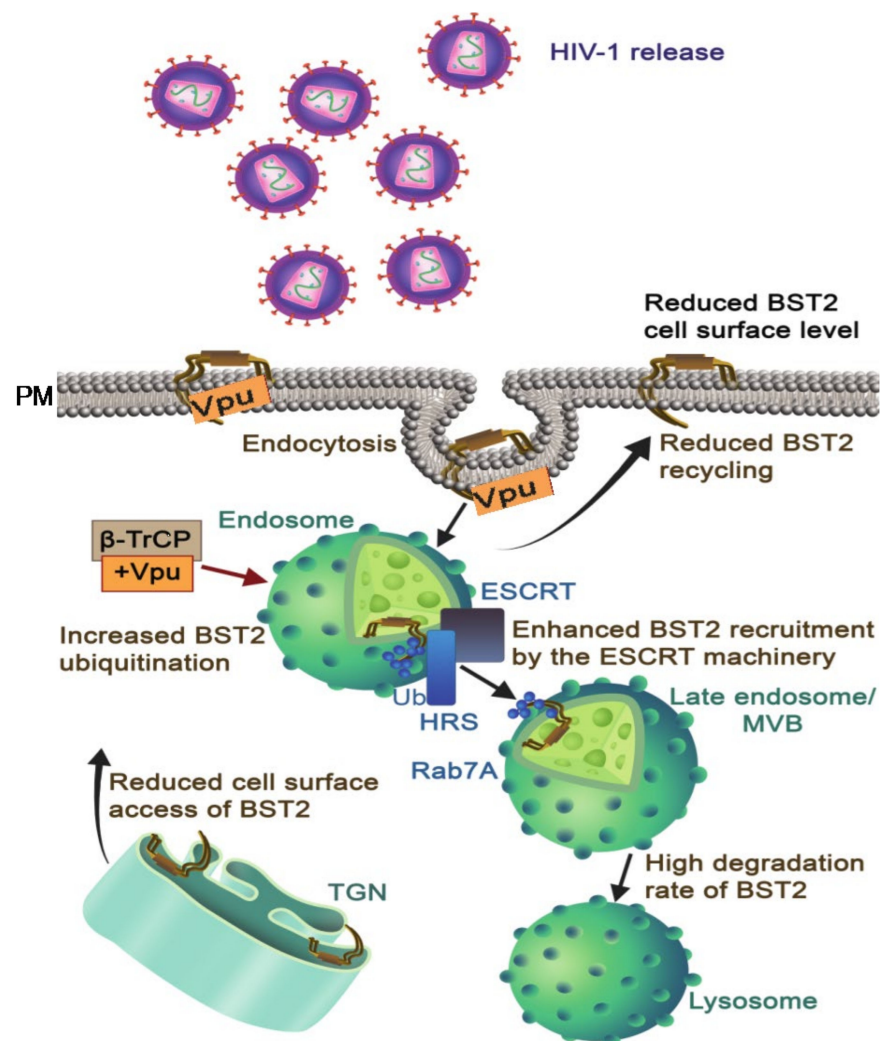


Figure 3. BST-2 surface downregulation and degradation by Vpu: In the absence of Vpu, BST-2 restricts newly synthesized viruses at the cell membrane, but Vpu downregulates BST-2 from the cell surface and promotes the release of virus particles from HIV-1-infected cells and enhances ubiquitination and lysosomal degradation of BST-2 by recruiting β -TrCP and exploiting the ESCRT pathway (ESCRT, HRS, and Rab7A). Besides, Vpu restricts BST-2 trafficking to the cell membrane from TGN and endosomes to reduce BST-2 level on the cell surface (indicated by arrows). Abbreviations: Vpu: viral protein U, BST-2: bone marrow stromal antigen 2, β -TrCP: β -transducin repeats-containing proteins, ESCRT: endosomal sorting complexes required for transport, Ub: ubiquitination, HRS: hepatocyte responsive serum phosphoprotein, MVB: multivesicular bodies, Rab7A, Ras-related protein 7A, TGN: trans-golgi network.

4.3. Immune Evasion to Virus Fitness and Survival

Innate immune responses play a significant role in host defenses against viral infections. Innate immune cells like natural killer (NK) and dendritic cells respond to invading viruses and contribute to controlling viral infection and replication during the initial stages of infection [92–94]. However, Vpu stabilizes HIV-1 infection and replication by evading immune responses by CD1d and NTB-A downmodulation [42,54]. Vpu also downregulates MHCII molecules from the cell surface to inhibit antigen presentation [39]. Together, these responses help HIV-1-infected cells escape cytotoxic and natural killer cells' ability to kill the infected cell.

4.4. Cell Death

Vpu protein can be cytotoxic. It induces cell stress through induction of Fas ligand, p53 stabilization, and activating JNK signaling pathways [40,95–97]. Oxidative stress may also contribute to cell death because Vpu induces oxidative stress by stabilization of p53 protein, increasing TGF- β protein levels and increasing the release of cytotoxic substances from HIV-1-infected cells [40,98–100]. NADPH oxidase plays fundamental roles in the generation of reactive oxygen species (ROS) and can induce cell death [101–103]. P67phox, a subunit of NADPH oxidase enzyme, has TPR repeat sequences including the Vpu-interacting partner SGTA [104,105].

4.5. Regulation of Ion Channel Activity

Vpu can oligomerize its transmembrane domain and form pentamer ion channel pores selective for monovalent cations [16,24,26]. Vpu ion channel activity is regulated by serine (S23) amino acids that are conserved in HIV-1 M group viruses [106,107]. TASK-1, a mammalian two-pore potassium channel protein with structural homology protein to Vpu, stabilizes cell membrane potential [108,109]. Vpu interacts with TASK-1 proteins, inhibits its ion channel activity, and depolarizes plasma membranes to enhance cellular secretions [108–110].

4.6. Vpu Effects on HIV-1 LTR Activity

HIV-1 gene activation is dependent on host transcription factors including NF- κ B, NFAT, and Ap-1 [111]. Vpu and its structural homolog TASK-1 inhibit transcription of unintegrated HIV-1 DNA in an NF- κ B-dependent manner [112]. Vpu mutants (replaced transmembrane domain of Vpu with its structural homologs) also suppress virus production by reducing LTR activity by an unknown mechanism [112,113]. Thus, Vpu appears to be capable of regulating LTR activity to control virus production in infected cells possibly through the involvement of zinc finger proteins and histone deacetylase (HDAC) [114–116].

4.7. Vpu Effects on Endolysosomes

Vpu protein is localized to plasma membranes, ER, TGN complex, and endosomes [27,29]. Endosomes fuse with lysosomes and generate endolysosomes, which play crucial roles in physiological and pathological conditions such as antigen presentation, membrane trafficking, metabolism, autophagy, viral infections, cancer, neurological complications, and metabolic disorders [31,117–126]. Endolysosomes are highly acidic organelles and this acidity is regulated by the proton pump v-ATPase [127–129], BK channels [130], TRPML1 channels [130], and two-pore channels [131]. Vpu interacting protein ATP6V0C is a subunit of the v-ATPase pump and promotes intracellular aggregation of BST-2 and contributes to HIV-1 release [132]. However, much is still unclear about the effects of Vpu on v-ATPase, endolysosome acidification, endolysosomes' regulatory functions, membrane trafficking, and autophagy.

Autophagy can enhance virus release and secretions from infected macrophage or monocyte cells [133–135]. HIV-1 enhances autophagy, while HIV-1 Nef blocks autophagy by direct interactions with Beclin and TFEB sequestration [136,137]. However, very little is currently known about the effects of Vpu on endolysosome degradation or autophagy pathways.

5. Conclusions

Vpu is an HIV-1 protein that counteracts host factors crucial for disseminating virus and disease progression. The primary targets of Vpu are cell surface host proteins that promote ubiquitination and proteasomal degradation processes [138–140]. Vpu might be targeted therapeutically to block the formation of heterooligomeric interactions between Vpu and host proteins at the cell surface as well as to suppress the progression of HIV-1 infection [141]. Moreover, Vpu disturbs the ubiquitination of host proteins by interacting with cellular factor β -TrCP through the cytosolic DSGxxS motif [138].

Hence, the transmembrane domain and DSxxSG motif in the cytosolic domain of Vpu may be targeted therapeutically against HIV-1 infection and disease progression.

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
AP-1	Activator protein 1
AP2	Adaptor complex 2
ATF4	Activating transcription factor 4
ATP6V0C	ATPase H ⁺ transporting V0 subunit C
BAG6	BAG cochaperone 6
β-TrCP	Beta-transducin repeats-containing proteins
BK channel	Big-potassium channel
BST-2	Bone marrow stromal antigen 2
CCR7	CC-chemokine receptor 7
CD1d	Cluster differentiation 1d
CD317	Cluster of differentiation 317
CD4	Cluster of differentiation 4
CK-2	Casein kinase 2
COS	CV-1 (simian) in origin
ER	Endoplasmic reticulum
ERAD	Endoplasmic reticulum-associated degradation pathway
ESCRT	Endosomal sorting complexes required for transport
Gp120	Glycoprotein 120
Gp41	Glycoprotein 41
GPI	Glycosylphosphatidylinositol
HDAC	Histone deacetylase
HEK293T	Human embryonic kidney 293 cells containing SV40 T-antigen
HELA	Henrietta lacks cells
HIV-1	Human immunodeficiency virus 1
HIV-2	Human immunodeficiency virus 2
Hrs	Hepatocyte responsive serum phosphoprotein
IFN-α/β	Interferon-alpha/beta
JNK	Jun N-terminal kinase
LTR	Long terminal repeat
MHC I and MHC II	Major histocompatibility complex I and II
MVB	Multivesicular bodies
NADPH oxidase	Nicotinamide adenine dinucleotide phosphate oxidase
NBR1	Neighbor of BRCA1 gene 1
NDP52	Nuclear dot protein 52
Nef	Negative factor
NFAT	Nuclear factor of activated T-cells

NF-κB	Nuclear factor kappa light chain enhancer of activated B cells
NPL4	Nuclear protein localization protein 4
NTB-A	Natural killer T- and B-cell antigen
ORF	Open reading frame
p67-phox	P67 phagocyte oxidase
PM	Plasma membrane
Rab7	Ras-related protein 7
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SCF	Skp1-Cullin-F-box protein
SIV cpz	Simian immunodeficiency viruses from chimpanzee
SIV	Simian immunodeficiency viruses
SIVagmTAN monkeys	Simian immunodeficiency virus from African green tanzanian monkeys
SIVdent	Simian immunodeficiency virus from Dent's mona monkey
SIVgor	Simian immunodeficiency virus from gorilla
SIVgs	Simian immunodeficiency virus from greater spot-nosed monkey
SIVmac	Simian immunodeficiency virus from rhesus macaques
SIVmon	Simian immunodeficiency virus from mona monkey
SIVsmm	Simian immunodeficiency virus from sooty mangabey
SGTA	Small glutamine-rich tetratricopeptide repeat
TASK-1	TWIK-related acid-sensitive K-1
TFEB	Transcription factor EB
TGF-β	Transforming growth factor-beta
TGN	Trans-Golgi network
TMD	Transmembrane domain
TPR	Tetratricopeptide repeat
TRPML-1	Transient receptor potential channel-1
Ub	Ubiquitination
UFD1L	Ubiquitin fusion degradation 1-like
V-ATPase	Vacuolar-type ATPase
VCP	Valosin-containing protein
Vpu	Viral protein U

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