HIV Accessory Proteins and Surviving the Host Cell

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Human immunodeficiency virus generates the accessory proteins Nef, viral infectivity factor (Vif), viral protein R, and viral protein U or viral protein X during viral replication in host cells. Although the significance of these accessory proteins is often lost in vitro, they are essential for viral pathogenesis in vivo. Therefore, these proteins have much potential as antiviral targets. Recent data reveal Vif perturbs an ill-defined antiviral pathway in host cells allowing HIV replication. These data highlight a common feature among HIV accessory proteins in manipulating the host to aid viral pathogenesis. Therefore, these new insights into Vif and other HIV accessory proteins are reviewed, emphasizing host cell interactions and new targets for therapeutic intervention.

Introduction

Human immunodeficiency virus codes six proteins, in addition to the structural Gag, Pol, and envelope (Env) proteins of all retroviruses. The regulatory proteins Tat and Rev are essential for viral replication by controlling HIV gene expression in host cells. In contrast, viral infectivity factor (Vif), viral protein R/viral protein X (Vpr/Vpx), viral protein U (Vpu), and Nef are often dispensable or accessory for viral replication in vitro. HIV isolates divide into two subtypes (HIV-1 and HIV-2), distinguished by the complement of accessory proteins. Both subtypes produce Nef, Vif, and Vpr. However, HIV-1 is unique for Vpu, whereas Vpx is only found in HIV-2, reflecting their zoonotic origin from simian immunodeficiency virus in chimpanzees or sooty mangabeys, respectively [1]. Although the relevance of accessory proteins may be obscure in vitro, they are essential for viral pathogenesis in vivo. Therefore, accessory proteins have pivotal roles for HIV not appreciated with many in-vitro systems.

This role of accessory proteins in HIV pathogenesis renders these proteins attractive targets for antiviral therapy. Understanding their functions and functional domains may reveal new virus-specific targets that can be exploited to block viral pathogenesis in vivo. Since reviewing the function of these proteins recently, rapid advances in the field reveal Vif overcomes a previously unknown antiviral pathway in host cells [2]. Therefore, Vif is similar to the other HIV accessory proteins in perturbing the host environment to benefit the virus. This supports the notion that although structural HIV proteins provide the building blocks for making new virions, the accessory proteins manipulate the host to allow HIV to survive and thrive in the hostile host environment. Therefore, the function of the HIV accessory proteins is updated to include these breakthrough insights into Vif, along with new revelations regarding Vpu and Nef. Because of space constraints, Vpr/Vpx is not discussed in this paper [2].

Viral Infectivity Factor

The 23-kDa Vif is traditionally the most poorly understood of all the HIV accessory proteins. Characterized as improving the infectivity of HIV virions, the precise mechanism underlying this critical function of Vif has, until recently, been elusive [3].

Early studies in cell culture systems provided initial clues regarding the mechanism of action of Vif, with reports that only particular cell types needed Vif for HIV replication. For instance, the natural in-vivo targets of HIV infection, $CD4^+$ T cells, and macrophages are nonpermissive, needing Vif for efficient viral replication. In contrast, common cell lines, such as HeLa, 293T, Jurkat, and SupT1, are permissive and do not need Vif for HIV replication [4]. Vif acts in the producer cell, but its effect on viral infectivity is manifested in the target cell where Vif promotes reverse transcribed HIV cDNA to accumulate and integrated cDNA to form [5]. Further studies demonstrate that Vif interacts with the viral RNA genome, protease, Gag precursor protein, cell membrane, and vimentin cytoskeleton in producer cells and is packaged into virions [6]. Although, how these activities improve viral infectivity in target cells was unclear and did not explain why only some cell types needed Vif for HIV replication.

A breakthrough in understanding Vif came in 1998 when the difference between permissive and nonpermissive cells was explored. When permissive and nonpermissive cells were fused, Vif-deleted virions from these heterokaryons had poor infectivity [7,8]. This result was consistent with nonper-

missive cells containing an inhibitory factor/pathway transferred to the permissive cells in the heterokaryons that prevented the Vif-deleted virions from being infectious. Therefore, Vif was improving viral infectivity by overcoming this inhibitory factor/pathway in nonpermissive cells, sparking the search for these inhibitory factors.

A protein fitting all the criteria expected for an inhibitory factor in nonpermissive cells was discovered in 2002, changing the face of Vif research [9••]. The use of subtractive hybridization allowed this inhibitory factor (CEM15; *ie*, APOBEC3G [apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G]) to be identified in the nonpermissive T-cell line CEM [9••,10]. APOBEC3G was not only present and absent in nonpermissive and permissive cells, respectively, but expressing APOBEC3G in permissive cells converted them to a nonpermissive phenotype. Furthermore, APOBEC3G in producer cells impaired HIV-1 infectivity in a dose-dependent manner that could be overcome by Vif coexpression, which implied that Vif acts to overcome the antiviral action of APOBEC3G to produce infectious virus [9••].

APOBEC3G belongs to a family of cytidine deaminases that deaminate or remove the amino group from cytosine bases creating uracil bases [10]. APOBEC family members can deaminate cytosine in RNA and DNA contexts, with APOBEC3G capable of mutating DNA in bacterial assays [10,11]. As APOBEC3G is packaged into HIV-1 virions, APOBEC3G from producer cells was speculated to modify the viral nucleic acid to block HIV-1 replication in target cells [9••]. A flurry of papers 9 months later confirmed that APOBEC3G was not acting on the viral RNA genome but, instead, was acting on the HIV-1 cDNA reverse transcribed from the genomic RNA in target cells [12,13•,14]. APOBEC3G was deaminating cytosine bases in the first cDNA strand reverse transcribed (minus strand) causing massive G-to-A hypermutation in the second cDNA strand reverse transcribed (plus strand; Fig. 1). The hypermutation occurred in hot spots on the reverse transcribed HIV cDNA, commonly at multiple G nucleotides in the plus strand [13•,14]. Furthermore, the G-to-A hypermutation mapped to zinc-binding motifs in APOBEC3G that are found in other APOBEC3G family members and mediates APOBEC1 deamination activity [13•,14,15]. The APOBEC3G-induced hypermutation correlated with impaired viral infectivity, and expressing Vif in the nonpermissive producer cells minimized the APOBEC3G-induced hypermutation [12,13•,14]. Therefore, Vif was improving HIV-1 infectivity by impeding the cytidine deaminase activity of APOBEC3G, permitting viral replication in target cells.

This APOBEC3G-induced hypermutation is not specific to HIV-1 because human APOBEC3G has the identical effect on retroviral particles from simian immunodeficiency virus and more distantly related equine infectious anemia virus and murine leukemia virus [13•,16]. Furthermore, APOBEC3G is not confined to humans, having orthologs in simians and rodents [17•]. In many instances, these rodent and simian APOBEC3G orthologs also block HIV-1 infectivity [17•]. This blockage suggests APOBEC3G comprises part of an innate defense mechanism against infectious nucleic acid that has been conserved in cells during evolution. Although HIV-1 Vif can block human APOBEC3G, it cannot stop the activity of most rodent or simian APOBEC3G [17•]. This may explain, in part, why HIV-1 replication is restricted to humans and why simian and rodent models of HIV have been difficult to generate.

However, it is still unclear how cytidine deamination of HIV-1 cDNA by APOBEC3G leads to the failure of HIV to generate integrated provirus in target cells. Studies agree that introducing uracil into reverse transcribing HIV-1 cDNA by APOBEC3G cytidine deamination or perturbing deoxynucleoside triphosphate pools does not affect minus-strand cDNA synthesis [17•,18,19]. Furthermore, although an in-vitro study using altered deoxynucleoside triphosphate pools suggests uracil in HIV-1 cDNA impairs plus-strand synthesis, two separate studies using endogenous reverse transcription or directly measuring viral cDNA in infected cells found APOBEC3G deamination only caused a minor reduction in plus-strand synthesis [17•,18,19]. However, APOBEC3G deamination greatly impaired the level of integrated provirus [17•]. This result suggests APOBEC3G-induced deamination has little effect on minus- or plus-strand cDNA synthesis, but it does alter the activity of the completed cDNA before or at integration into the cell genome to block HIV replication.

Major progress in understanding how HIV-1 Vif overcomes the antiviral activity of human APOBEC3G has also been made. Although HIV-1 Vif and APOBEC3G can be packaged into virions, Vif expression in producer cells impairs the ability of APOBEC3G to enter virions [17•,20–23,24••,25]. This impairment correlates with a reduction in steady-state levels of APOBEC3G in the cells. Vif directly binds APOBEC3G, and most studies agree that Vif reduces the half-life of APOBEC3G by targeting APOBEC3G for ubiquitination and degradation through cellular proteasomes [20–22,24••,25,26]. The most complete study implies that Vif acts as an adaptor, not only binding APOBEC3G but also recruiting an E3 ubiquitin ligase complex (comprised of cullin 5, elongin B, elongin C, and Rbx1 proteins) using the highly conserved SLQXLA motif in lentiviral Vifs [24••]. Recruiting the complete E3 ubiquitin ligase complex to HIV-1 Vif correlates with ubiquitination and proteasome degradation of APOBEC3G [24••]. Two studies also suggest that Vif may reduce intracellular APOBEC3G levels by decreasing the rate of APOBEC3G synthesis, specifically at translation [20,23]. However, Vif induces rapid degradation of APOBEC3G within minutes of APOBEC3G synthesis [21,25]. Therefore, rapid APOBEC3G degradation may complicate this apparent reduction in APOBEC3G synthesis. These data collectively infer that Vif prevents APOBEC3G incorporation into virions through targeting APOBEC3G for rapid degradation through proteasomes, thus diminishing the intracellular pool of APOBEC3G in producer cells available for packaging into virions.

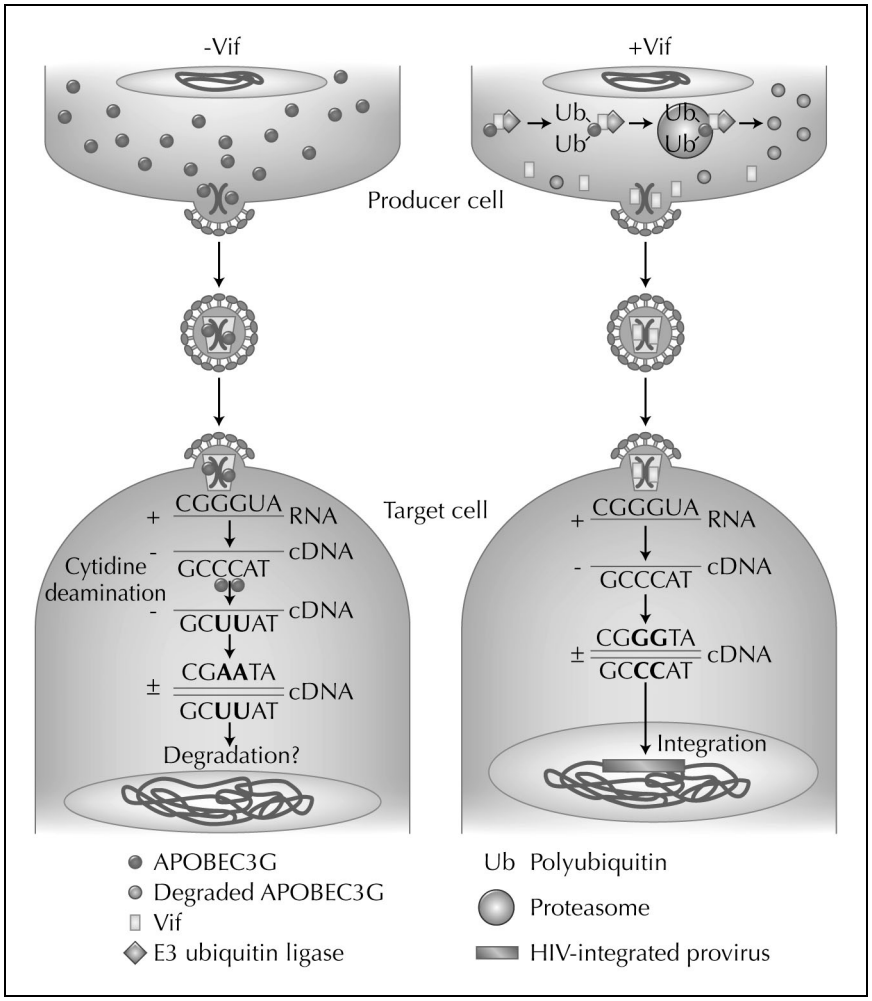

Figure 1. A model of Vif interplay in the APOBEC3G antiviral response. In producer cells containing APOBEC3G but lacking Vif (*left panel*), APOBEC3G is packaged into virions. These virions bind and enter target cells in which reverse transcription of the viral RNA into cDNA ensues. APOBEC3G deaminates cytosine (C) bases in the minus (-) cDNA strand creating uracil (U). This uracil base is read as thymine (T) during reverse transcription and deoxyadenosine is incorporated into the complementary plus (+) cDNA strand, which results in guanosine (*bold G in right panel*) to adenosine (*bold A in left panel*) mutations in the plus cDNA strand. The fate of this hypermutated HIV cDNA is unknown, but it has limited ability to integrate into the host cell genome and is likely degraded. In producer cells expressing APOBEC3G and Vif (*right panel*), Vif binds to APOBEC3G and an E3 ubiquitin ligase complex, which polyubiquitinates APOBEC3G for degradation by the cell proteasome and prevents APOBEC3G incorporation into virions in which Vif is packaged. The failure to incorporate APOBEC3G into virions blocks the deamination of cytosines in the reverse transcribed minus-strand cDNA, thus blocking G-to-A hypermutation in the plus-strand cDNA. Consequently, the virions are infectious and the viral cDNA moves into the nucleus for integration into the cell genome and subsequent viral replication.

Overall, this research supports the model for how Vif improves HIV infectivity by overcoming the APOBEC3G antiviral response (Fig. 1). In the absence of Vif, APOBEC3G is incorporated into virions, which leads to cytidine deamination and hypermutation of the reverse transcribed viral cDNA in target cells, thus limiting the formation of integrated HIV cDNA in the target cell genome by an undisclosed mechanism, impeding HIV replication. Conversely, the presence of Vif in producer cells targets APOBEC3G for rapid degradation through proteasomes, limiting the intracellular pool of APOBEC3G available for virion incorporation, which impedes APOBEC3G incorporation into virions, thus preventing APOBEC3G-induced hypermutation of the viral cDNA in target cells and allowing viral replication to proceed. Therefore, the HIV virions are infectious. Identifying the domains in Vif that cause APOBEC3G degradation, such as the SLQXLA motif, may reveal new antiviral targets to block this detrimental effect of Vif on the host cell and curb HIV infectivity in vivo [24••].

Viral Protein U

The 16-kDa Vpu unique to HIV-1 is a type 1 integral membrane protein that configures into two domains [27]. The N-terminal transmembrane domain anchors Vpu to cell membranes while the hydrophilic C-terminal domain lines the cytoplasmic surface of the membrane [28]. Vpu is not found within virions, but it acts within host cells to perform two main functions: enhancing virus particle release and downregulating intracellular CD4. In both functions, Vpu manipulates the host cell environment to benefit the virus, promoting virion output or maximizing virion infectivity.

Enhancing virus particle release

The ability of Vpu to enhance virion release from infected cells remains poorly understood [27]. This function maps to the N-terminal transmembrane domain of Vpu involved in oligomerisation [29]. Oligomerisation of Vpu forms ion channels [28]. Therefore, Vpu ion channels at the cell surface membrane may accelerate virion release by changing membrane potentials to favor particle release or promote membrane fusion [28]. Alternatively, Vpu ion channels may alter ion levels to aggregate lipid rafts at the plasma membrane through which HIV-1 virions selectively bud, thus facilitating virion release [30].

The effect of Vpu on virion release depends on the origin of the producer cell. For instance, most human cells,

including T cells and macrophages, require Vpu for efficient virion release. Conversely, HIV-1 particles can efficiently release from many simian cell types without Vpu [31••]. This effect suggests human cells may contain a restriction to virion release that is absent in simian cells. Analyzing the release of HIV-1 virions from human and simian cell fusions tested this hypothesis. The fusion of different human cell lines to a simian Cos cell line impaired virion release from the heterokaryons without Vpu. Furthermore, expressing Vpu in the heterokaryons elevated virion release [31••]. This demonstrates that human cells contain an inhibitory pathway that is transferred to simian cells in the heterokaryons, limiting HIV-1 virion release. Furthermore, Vpu is able to overcome this human cell restriction to accelerate virion release. The nature of the human cell restriction remains unclear, but it may involve the cellular Vpu-binding protein, which prevents Vpu from enhancing virion release when over expressed [32]. Therefore, understanding the nature of the discovered human cell restriction to virion release and characterizing Vpu domains that overcome this restriction may reveal new targets in Vpu for antiviral therapy.

Downregulating intracellular CD4

Viral protein U has a key activity in degrading intracellular CD4 [29]. HIV Env protruding from the surface of virions initially binds the CD4 antigen on target cells, initiating viral infection of the cell. During viral replication, once inside the infected cell, the Env glycoprotein-160 precursor and CD4 proteins translate into the endoplasmic reticulum. In the cells lacking Vpu, the Env precursors complex with CD4 in the endoplasmic reticulum, downregulating the expression of both proteins at the cell surface, which prevents Env from being incorporated into new assembling virions, producing noninfectious virus. However, Vpu binds CD4 in the Env precursor CD4 complexes and recruits the human β-transducin repeat-containing protein (h-βTrCP). This h-βTrCP recruits the ubiquitin/proteasome pathway, targeting CD4 for degradation, which releases the Env precursor for subsequent processing and expression at the cell surface for incorporation into assembling virions [29]. Therefore, Vpu acts as an adaptor, linking intracellular CD4 molecules to the ubiquitin/proteasome pathway for CD4 degradation.

This host cell manipulation benefits HIV by promoting the expression of intracellular viral Env protein at the cell surface for incorporation into assembling virions, improving viral infectivity [29]. Furthermore, CD4 at the cell surface can bind Vpu in the plasma membrane, inhibiting Vpu-mediated virion release by possibly blocking Vpu oligomerisation into ion channels [33]. Therefore, downmodulating CD4 from the surface of infected cells may have dual benefits, promoting the Vpu-mediated release of virions and increasing Env expression at the cell surface for virion incorporation. Sequestering h-βTrCP to Vpu for CD4 degradation can perturb the levels of other cellular proteins relying on h-βTrCP for proteasome degradation [34]. For instance, Vpu expression impedes IκB-α degradation, elevating IκB-α levels in cells [29]. As IκB-α blocks the activity of nuclear factor-kappaB, which participates in regulating cellular apoptosis and possibly innate immune defenses, Vpu interplay in the h-βTrCP–proteasome pathway may have secondary effects on other cellular proteins to further influence viral pathogenesis [29,35].

Human immunodeficiency virus-1 is the more widespread virulent subtype underlying the current HIV pandemic. Vpu is unique to HIV-1 but omitted in HIV-2, which implies an important role for this accessory protein in elevating the virulence of HIV-1. The ability of Vpu to manipulate the host cell by two separate methods (*eg*, overcoming a human cell restriction to enhance virion release and degrading CD4 to improve virion infectivity) may facilitate HIV-1 virulence. However, these dual functions of Vpu may also reveal its weakness, providing multiple targets for antiviral intervention and more opportunity to block Vpu function and its impact on pathogenesis.

Nef

Nef is an important factor for HIV disease pathogenesis in vivo [36,37]. Nef is the first HIV protein expressed in infected cells and is myristoylated at the amino terminus, which targets Nef to cell membranes [38]. This 27-kDa form of Nef is packaged into virions, in which it can be cleaved by the viral protease producing a 20-kDa form that lacks the 7-kDa amino terminus and myristoylation signal [39]. Nef was originally described as a negative factor for viral replication, but later emerged as a positive factor in vivo, containing several effector functions and a more accurate meaning for the Nef acronym [40]. Among the vast number of studies, three predominant roles have emerged for Nef that all manipulate the host cell environment.

Perturbing endosome trafficking pathways

Nef interferes with endosome trafficking pathways in infected cells, thus altering the expression of multiple membrane proteins that use these endocytic pathways. For instance, the expression of CD4, major histocompatibility complex (MHC) classes I and II, CD28, tumor necrosis factor, LIGHT, and dendritic cell-specific ICAM-3 grabbing nonintegrin are all altered by Nef [41]. Nef uses at least two distinct mechanisms to perturb these endosomal pathways, exemplified by downmodulation of CD4 and MHC I from the cell surface.

To downmodulate CD4, Nef acts as an adaptor. Nef binds cell surface CD4 at its N-terminus and uses dileucine plus diacidic motifs in its C-terminus to recruit adapter protein-2, which targets CD4 to endosomes for subsequent lysosome degradation [42,43]. Recently, this ability of Nef to degrade CD4 has been correlated with improving HIV replication in primary T cells and mediating disease pathogenesis in mouse models [44,45]. Therefore, CD4 degradation by Nef appears to be a major factor in HIV pathogenesis.

Nef also downregulates a subset of MHC class I molecules (*ie*, HLA-A and HLA-B) from the surface of infected cells by linking these molecules to an endocytic pathway distinct from CD4. Nef binds the cytoplasmic tail of these MHC I molecules and recruits phosphofurin acidic cluster sorting protein-1, which redirects these proteins from the cell surface back to the trans-Golgi network through an endosome pathway [46,47]. Nef does not target MHC I to lysosomes for degradation, unlike CD4. Nef may also disrupt the transport of HLA-A and HLA-B from the trans-Golgi network back to the plasma membrane to keep MHC I expression diminished at the cell surface [48]. HLA-A and HLA-B are important molecules in immune surveillance, presenting antigen on cells that are recognized for destruction by cytotoxic $CD8^+$ T cells. Therefore, downregulating HLA-A and HLA-B helps HIV-1 infected cells evade recognition and destruction by cytotoxic $CD8^+$ T cells, perhaps facilitating HIV persistence in the host [49,50].

Modulating signal transduction

Nef has a complex role modulating signal transduction pathways in HIV-infected cells [38,42]. Nef interacts with an array of signal transduction proteins [42,51]. Many of these interactions emanate from the proline-rich region of Nef, which binds Src homology-3 domains prevalent in many signal transduction proteins. As Nef interacts with many signaling proteins in multiple pathways, often with contrasting effects in several papers, understanding the importance of all of these interactions for Nef function is challenging. However, amidst the many studies, Nef interplay in cellular signal transduction pathways appears to have important effects on T-cell activation, apoptosis, and migration [2,52]. Furthermore, a new consequence of Nef-mediated signaling has been recently proposed for HIV-1 infected macrophages [53••].

Although most experiments examine the role of Nef in cell signaling using de novo-synthesized Nef, exogenous Nef released into the extracellular milieu during infection may also alter signal transduction in surrounding cells [54]. Exogenous Nef enters primary T cells and promonocytes by endocytosis after nonspecific binding to the cell surface. This source of Nef can activate the JNK signaling protein, stimulate the expression of nuclear factor-kappaB, and enhance viral replication in chronically infected promonocytic cells [54]. Therefore, the signal transduction effects of exogenous Nef on surrounding cells may alter HIV pathogenesis, stimulating viral replication in latent reservoirs of virus infection and priming uninfected cells for efficient replication.

Enhancing viral infectivity

Nef increases HIV infection in single-cycle infectivity assays, although the mechanism underlying this phenomenon remains controversial [42]. Reminiscent to Vif, Nef acts in the virus-producing cell to improve virion infectivity in the target cell [55]. The ability of Nef to enhance virion infectivity is dependent on the pathway of viral entry. Nef improves the infectivity of virions when fusion takes place on the cell surface, mediated by Env proteins from HIV and murine leukemia virus. In contrast, Nef no longer improves the infectivity of HIV virions pseudotyped with vesicular stomatitis virus G or Ebola virus glycoproteins, which enter cells through endosomes. For these glycoproteins, fusion takes place after acidification of the endosome, releasing the virion core into the cytoplasm [56].

Although several hypotheses have been put forth to explain this Nef phenotype, recent data indicate that Nef does not improve viral infectivity through effecting the viral matrix protein, the stability or structure of the viral core, and is not influenced by the viral chemokine coreceptor used for entry [39,57,58]. Furthermore, Nef does not improve infectivity by enhancing the fusion of wild-type HIV virions with target cells because recent studies using a new fusion assay demonstrate that HIV lacking Nef fuse to target cells normally [59,60]. Conversely, the ability of Nef to enhance virion infectivity does require Nef to bind the plasma membrane in the producer cell because myristoylation-defective Nef no longer enhance virion infectivity [61]. Once inside the target cell, virion-associated Nef remains localized with the viral core and internal ribonucleoprotein complex [39]. Therefore, Nef may act on viral infectivity inside the target cell in association with the viral core.

A new model has been proposed to explain how Nef stimulates HIV infectivity [60]. This model is based on the fact that disrupting the actin cytoskeleton in target cells can restore the infectivity of Nef-deficient virions. In this model, disrupting the actin cytoskeleton may disrupt the cortical actin barrier, a dense network of actin filaments located just beneath the plasma membrane. This cortical actin is known to impede the entry of intracellular pathogens into the cell cytoplasm and could similarly obstruct the passage of HIV genomes into the cytoplasm after fusion at the cell surface. This model also explains why envelopes that mediate entry through endocytosis can complement Nef-deficient HIV because these endosomes naturally penetrate the cortical actin barrier to move their substrates into the cytoplasm. The model is also consistent with interactions between Nef and proteins known to reorganize the actin cytoskeleton, such as p21 activated kinase and Vav. These Nef-interacting proteins may induce local reorganization of the cortical actin barrier, easing the movement of HIV genomes into the cytoplasm after fusion and causing Nef to increase HIV infectivity [60]. Although further study is needed to test this model, it is compelling because it can also explain observations from other researchers regarding the role of Nef in HIV infectivity. Therefore, Nef has an additional role in host cells aside from interfering in endocytic pathways and modulating signal transduction to perhaps reorganize the cell actin cytoskeleton to favor HIV infection.

Nef is an important determinant of HIV pathogenesis in vivo, although how Nef accelerates disease progression remains unclear [36,37]. Downregulating important

immunologic molecules, such as CD4 and MHC I, while interfering with T-cell activation, will likely impair host immune responses to facilitate viral pathogenesis. The ability of Nef to reduce CD4 was reported to be key for viral pathogenesis in mouse models [45]. A recent study also suggests that Nef may influence HIV reservoirs to affect pathogenesis [53••]. Expressing Nef in macrophages increased the infection of T cells in mixed-cell cultures by stimulating the secretion of soluble ICAM and CD23. These soluble factors activated B cells that stimulated resting T cells to become susceptible to viral infection [53••]. Therefore, Nef may expand the cellular reservoirs of HIV infection to resting T lymphocytes, and these combined functions of Nef likely accelerate disease progression by altering the pathogenesis at multiple levels. Therefore, Nef may offer many antiviral targets to block viral pathogenesis in the host.

Conclusions

Human immunodeficiency virus accessory proteins exhibit a common feature in altering the host cell environment to facilitate viral replication within host cells, the infectivity of virions subsequently released, or limit host antiviral responses. This feature likely underlies the success of accessory proteins in promoting HIV pathogenesis in vivo. However, this ability of accessory proteins to perturb host cells by diverse means may also be their Achilles heel, exposing more virus-specific targets to impede HIV pathogenesis in vivo. For instance, viral motifs that allow Vif to overcome the APOBEC3G antiviral response or Vpu to overcome a human cell restriction to virion release could be blocked, favoring these cellular defenses and disrupting viral progress. Therefore, accessory proteins offer much promise as antiviral targets to limit HIV pathogenesis. With viral resistance and side effects limiting current anti-HIV drug regimens, a new line of anti-HIV drugs aimed at viral pathogenesis would be welcome relief for afflicted patients.

Acknowledgment

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This paper provides the most complete picture to date for how Vif overcomes the antiviral activity of APOBEC3G. It defines Vif as an adaptor, linking APOBEC3G to an E3 ubiquitin ligase complex that polyubiquitinates APOBEC3G for degradation by proteasomes. This rapid degradation impairs APOBEC3G incorporation into virions, thus preventing APOBEC3G from blocking viral infectivity in target cells.

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