The Role of HIV-1 Vif in SAPOBEC3G, A3G, Cellular core-binding factor β, G2 Cell Cycle arrest, causes Disruption immune system and in Progression of HIV-1infection, as potential target for vaccine development (Part Six-2)

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Abstract

Accessory proteins, thought initially to be dispensable for infection, have now been shown to be important for efficient infection in vivo.

HIV-1 Vif interacts with the cellular core-binding factor β (CBFβ) and counteracts the protective roles of certain human APOBEC3 (A3) proteins by targeting them for proteasomal degradation.

Recent evidence suggests that certain viral proteins, like Vif, have evolved to overcome the antiviral mechanisms of the host, while proteins like Nef, which are markers for disease pathogenesis in vivo, help to increase pathogenesis by targeting bystander cells.

Vif overcomes the innate antiviral activity of A3G by direct protein binding and promoting its degradation via the cellular ubiquitin/proteasomal pathway. Binding of Vif to A3G is essential for its degradation since disruption of this interaction is predicted to stimulate intracellular antiviral immunity.

Previous studies have identified some amino acids important for Vif–CBFβ interactions, and recently a co-crystal structure of a pentameric complex of HIV-1 Vif, CBFβ, Cul5, EloB, and EloC was resolved.

Recent study demonstrated that multiple Vif residues are involved in the extensive N-terminal Vif–CBFβ interaction and that the 5WQVMIVW11 region of Vif is the major determinant

In this article, I discuss the VIF biology; VIF is an Essential Regulator of HIV-1 Infection, APOBEC3 expression in cells of the immune system, Vif Inhibition of Cytoplasmic Defenses, Vif

Antagonize SAPOBEC3G, and The Interaction OF Vif with APOBEC3 Proteins, The Vif-A3G Interaction, A Novel Vif Function and Vif protein–protein interactions

Key Words: HIV-1 VIF, APOBEC3 Proteins, Vif-A3G, G2 Cell Cycle arrest, Innate immune, Adaptive immune Transcriptional Regulation, Repair and Vaccine

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1. Introduction

HIV-1 manipulates fundamental host cell processes in complex ways to achieve optimal replicative efficiency. The virus enters the cells via the envelope (Env) glycoprotein which binds the CD4 receptor along with the chemokine receptors CXCR4 or CCR5 (1),(2),(3),(4). The viral RNA is then reverse transcribed into proviral DNA in the cytoplasm, enters the nucleus as a pre-integration complex, and is integrated into the cellular genome. HIV-1 replication is tightly regulated at the transcriptional level through the specific interaction of viral proteins, which bind to target sequences in the viralRNA and profoundly affects viral expression (5),(6). Besides structural proteins, HIV-1 encodes accessory proteins, Nef (negative effector), Vif (viral infectivity factor), Vpr (viral protein r), and Vpu (viral protein u) (7). Vif is a 23-kDa cytoplasmic protein that is expressed from a partially spliced mRNA in Rev-dependent manner during the late phase of HIV-1 replication. The human immunodeficiency virus type 1 (HIV-1) Vif protein is essential for virus replication in primary lymphoid and myeloid cells, but is dispensable for efficient replication in several transformed T-cell lines as well as in nonlymphoid cell lines such as HeLa and 293T (8),(9),(10). HIV-1 and other lentiviruses encode the accessory protein Vif that counteracts the antiviral activities of APOBEC3 (A3) proteins and is required for infection and propagation in primary CD4+ T cells and in non-permissive T cell lines (for recent reviews see

Refs (11),(12). Vif neutralizes the inhibitory activities of A3 proteins by targeting them for polyubiquitination and proteasomal degradation by hijacking an E3 ubiquitin ligase complex (13). Jager et al. (14) and Zhang et al. (15), recently reported that in addition to binding to cullin 5 (Cul5) and elongin B/C (EloB/C), Vif binds to the cellular core-binding factor β (CBFβ), and the Vif–CBFβ interaction is essential for inducing efficient degradation of A3 proteins, which inhibit HIV-1 replication in non-permissive cell types. CBFβ is an evolutionarily conserved non-DNA binding component of the mammalian runt-related transcription factors (RUNX 1-3), which are critical in hematopoiesis, T cell differentiation, and skeletal development (16),(17). CBFβ is an allosteric regulator of RUNX proteins and has previously been reported to stabilize RUNX1 by preventing its ubiquitin-mediated degradation (18). Recently, CBFβ was proposed to play a critical role in stabilizing the intrinsically unstructured HIV-1 Vif and promoting formation of a well-ordered substrate receptor by facilitating local folding of the N-terminal Vif region (14),(15),(19). Several reports have established that HIV-1 Vif interacts with CBFβ and have shown that CBFβ depletion hampers virus replication in cells expressing A3 proteins primarily by interfering with Vif's ability to induce degradation of the A3 proteins (14),(15),(19). HIV-1 Vif associates with CBFβ in human cells and recombinant CBFβ enhances Vif's solubility, stability, and association with an E3 ubiquitin ligase complex (19),(20),(21),(22),(23). Vif directly interacts with substrate APOBEC3 proteins to recruit them to the E3 ligase (24). Of the seven A3 proteins expressed in humans, A3D, A3F, A3G, and A3H have been shown to possess true antiretroviral activity against HIV-1 (25). APOBEC3 proteins inhibit replication of HIV-1 lacking vif, which encodes a 23-kDa protein (26),(27),(28),(29),(30). In virus producer cells, Vif binds APOBEC3D, APOBEC3F, APOBEC3G, and APOBEC3H, targeting them for ubiquitinylation and degradation in the proteasome through interactions with a number of cellular factors, including CBF-b, Cul5, and elongins. This prevents APOBEC3 packaging and, thereby, overcomes the antiviral activity (31),(13),(32),(33),(34),(14). In contrast, in producer cells infected with vifdeficient HIV or with retroviruses that do not express a Vif protein, APOBEC3 proteins are packaged into virions via interaction with the nucleocapsid protein and viral RNA (35),(36),(37),(38),(39). The different APOBEC3 proteins are expressed at various levels in hematopoietic cell populations, including CD4+ and CD8+ T cell subsets (e.g., naive and memory), B cells, and myeloid cells (40),(41), (42). CD4+ T cell expression of APOBEC3 proteins clearly plays a role in virus restriction. Analysis of the deamination motifs found in HIV-1 cDNA isolated from CD4+ T cells indicates that APOBEC3G is the dominant antiviral protein in this cell type (43).

2. VIF Biology

The use of a *vif* mutant HIV-1 virion has proven extremely valuable for understanding Vif's contribution to viral infectivity (44),(10),(45),(46). The major cell types for infection, namely CD4+ T cells (primary and several T cell lines) and macrophages, are restrictive (non-permissive) for HIV-1 replication and require Vif for maintaining viral infectivity (47),(48),(8). Initial studies suggested that Vif was important for early events after virus entry but preceding or during the early stages of viral DNA synthesis, since *vif* mutants exhibited reduced RT activity *in vitro* and synthesis of early and late DNA products (44),(49). Vif is a 23 kD basic protein that is expressed late during infection in a Rev-dependent manner (44), and is largely localized within the cytoplasm (50),(51). Vif exists in a soluble cytosolic form that co-localizes with the intermediate filament vimentin (51), and can be found associated with intracellular membranes via its C-terminus, which is also essential for its function and multimerization

(50),(51),(52). Early reports found that Ser144, Thr155, and Thr188 are all phosphorylated *in vivo* by an as yet unidentified cellular kinase (53),(54). A later study observed that Thr96 and Ser165 are also phosphorylated by the p44/42 mitogen-activated protein kinase (also known as ERK1 and ERK2) (54). The importance of phosphorylation on Vif activity is exemplified when mutation of the phosphorylation site at Ser144 to an alanine resulted in a loss of activity and an almost complete inhibition of viral replication (53), Interestingly, a recent report by (55), observed that Vif was modified by ubiquitination suggesting another possible route that may influence the function of Vif. Low levels of Vif (1 to 40 molecules/virion) have been found to be packaged into newly synthesized progeny (51),(56),(57), however the significance of this event is not entirely clear. *vif* mutant HIV-1 virions exhibit structural abnormalities within the cone-shaped core. Electron-dense material was observed to be compacted at the broad end of the cone, while the narrow end appeared transparent (58). A recent report indicates that these *vif* defective cores were more susceptible to disruption by detergents, high salt, pH, and RNase than wild type virion cores (59). Vif increases the stability of virion cores, which may prevent premature degradation upon viral entry (59). The effect of Vif on nonpermissive cells, where it is critical for proviral DNA synthesis (10), is highly dependent on cellular factors with which Vif associates. Vif has been shown to bind to a number of cellular proteins, including Hck tyrosine kinase (Hck) (60), a component of the HIV-1 PIC, Ku70 (61); Sp140 nuclear protein (61); HP68 when bound to Gag (62), spermine/spermidine N1-acetyl-transferase (SSAT); vimentin; Triad 3; and a novel Vif-binding protein (NVBP) (63). It has also been shown that Vif binds to HIV-1 genomic RNA in the cytoplasm and forms a 40S mRNP complex that most likely mediates viral RNA interaction with HIV-1 Gag precursors (64). The HP68 protein is essential for the post-translational events in immature capsid assembly and may therefore be another route for Vif incorporation into virions (62). Hck is a tyrosine kinase that has been shown to inhibit HIV-1 production and consequent infectivity in vif defective virus, while having no effect on the wild-type virus (60); Therefore, Hck has cellular antiviral properties in non-permissive cells, which are subverted in the presence of Vif. The Ku70 protein, which is a component of the PIC, may allow for the recruitment of Vif to initiate proviral DNA synthesis. Since SSAT is involved in polyamine metabolism and polyamines are important in the reverse transcription process, the Vif-SSAT interaction most likely increases the efficiency of reverse transcription (63) Sp140 is an IFN-gamma-inducible protein that is both lymphocyte- and macrophage-specific and almost exclusively localized to nuclear bodies (65). Interestingly, it has been shown that Sp140 is found in all non-permissive cells and that Vif is able to partially localize Sp140 to the cytoplasm from the nucleus (61); CEM15 was shown to be a cytidine deaminase capable of inducing a guanine to adenine hypermutation in the plus-strand of newly synthesized viral DNA (66),(67). Since the main cell types infected by HIV-1 are nonpermissive cells, the presence of Vif most likely prevents the hypermutation activities of CEM15 and allows for the minimal introduction of mutations during reverse transcription. On the other hand, it is probable that in the presence of attenuated Vif and/or low levels of Vif, this endogenous inhibitor of HIV-1 may also serve to increase the variability of viral proteins and strains present during infection. Furthermore, (68),have recently shown that Vif prevents CEM15 encapsidation by impairing its translation, as well as hastening its post-translational degradation through ubiquitination and targeting to the 26S proteasome via its SLQ(Y/F)LA motif (33),(69). The antagonistic interaction of Vif with APOBEC-3G appears to be a promising avenue for rational drug design (70),(71),(72). While Vif is important in the later stages of the viral life cycle, Vpu is also important at late stages aiding in the release of infectious virions.

3. Location of Vif residues implicated in binding of APOBEC3 proteins

The role of a substrate receptor in an E3 ligase complex is to recruit a particular protein for polyubiquitylation through specific binding interactions. Vif targets several, albeit related, proteins of the APOBEC3 family. Specifically, Vif-dependent degradation of APOBEC3C, D, F, G and H (haplotype II), collectively referred to as the A3s, has been shown(25). APOBEC3 proteins share a common core fold (Box 2) but positive evolutionary pressures to adapt to endogenous and exogenous retro-elements led to expansion and diversification of the family. Thus, the APOBEC3 family does not have a single conserved surface to which Vif can bind and, as such, it is thought that Vif has evolved to recognize multiple surfaces presented by APOBEC3 family members. Some sequence motifs have been shown to be important for binding multiple APOBEC3 proteins, whereas others are implicated in binding only a single APOBEC3 member. Some of the conserved motifs implicated in binding A3G and A3F are either buried within the core fold of Vif or buried at the interface with CBFb.. Many of these residues map to the surface of Vif and are solvent exposed in the context of the E3 ubiquitin ligase complex structure, suggesting a direct role in binding of particular A3 proteins. These solvent-exposed, surface-mapped residues implicated in binding A3F and A3G form two distinct and contiguous, though partially overlapping, regions (73), Some Vif residues implicated in binding of A3F (and for A3G) are also partially buried at the interface with CBFb, suggesting an overlap between the binding interfaces of Vif for A3F and CBFb (74).

4. VIF is an Essential Regulator of HIV-1 Infection

it was recognized that the 192 amino acid HIV-1 Vif protein is a potent regulator of viral infection—hence its name, virion infectivity factor (75),(76),(77). Several key observations were made during this period that have helped enlighten future work, specifically: (i) an intact vif gene is required for pathogenic infections in the SIV/rhesus macaque system (78), (ii) Vif is critical for virus replication in some cells such as primary CD4 T cells and immortalized lines such as HUT78 or CEM (non-permissive cells), yet entirely dispensable in other T-cell lines such as SupT1 or CEM-SS (permissive cells) (58),(10). (iii) Vif acts in virus producing cells to regulate the quality, i.e. the infectivity, rather than the quantity of progeny virions (58),(10),(79). (iv) virions produced in the absence of Vif yield reduced levels of cDNA reverse transcripts following the challenge of susceptible target cells (46),(10),(45),(79); and (v) the stoichiometries and nature of the structural and enzymatic proteins (namely, Gag, Pol and Env) that are incorporated into nascent virus particles are not influenced by Vif (10),(57),(69).

5. APOBEC3 expression in cells of the immune system

The different APOBEC3 proteins are expressed at various levels in hematopoietic cell populations, including CD4+ and CD8+ T cell subsets (e.g., naive and memory), B cells, and myeloid cells (40),(41),(42). CD4+ T cell expression of APOBEC3 proteins clearly plays a role in virus restriction. Analysis of the deamination motifs found in HIV-1 Cdna isolated from CD4+ T cells indicates that APOBEC3G is the dominant antiviral protein in this cell type (43). Moreover, HIV-1 proviral DNA hypermutation combined with increased APOBEC3G expression levels was linked to lower virus replication and increased CD4+ T cells counts in patients (80),(81),

(82),(83). Although individuals carrying the anti–HIV-1 APOBEC3H Hap II allele also display lower levels of infection and higher CD4+ T cells counts compared with individuals carrying other APOBEC3H alleles (84). More recent work suggests that both cytidine deamination and reverse-transcription inhibition play a role in HIV-1 restriction in primary CD4+ T cells (43). Macrophages are also major targets of infection by HIV and other retroviruses, particularly at mucosal surfaces, serving not only as latent reservoirs but also as APCs (85). However, macrophages are relatively resistant to retrovirus infection due to the expression of APOBEC3 proteins, as well as additional cell host restriction factors, such as SAM domain and HD domain-containing protein 1; the latter is believed to deplete the dNTP pools available to reverse transcriptase for viral cDNA synthesis (86),(87),(88),(89). Macrophages express APOBEC3G, APOBEC3F, and APOBEC3DE, and their upregulation is IFN-a dependent, although APOBEC3G restricts HIV-1 more potently than the combined effect of APOBEC3F and APOBEC3DE in this cell type (42),(90). Target cell expression in primary macrophages may also play a role in restricting HIV, as well as other retroviruses (91),(92),(40). APOBEC3A is also expressed at high levels in monocytes, whereas fully differentiated macrophages express low levels (93), however, macrophage expression of APOBEC3A is strongly enhanced by IFN-a treatment (40),(42),(93). This difference in APOBEC3A levels between monocytes and macrophages correlates with susceptibility to HIV-1 infection, with monocytes being more resistant to infection than macrophages; when APOBEC3A was silenced in HIV-1–infected monocytes, virus production was increased (86),(93). APOBEC3G induction by IFN-a in CD14+ monocytes is also significantly higher in HIV-1–exposed but seronegative individuals than in HIV infected individuals or healthy controls (94). Transmission of virus from DCs to T cells likely occurs by direct cell–cell transmission via immunological synapses (95),(96). Activation of myeloid DCs by IFN-a results in the potent upregulation of APOBEC3A, APOBEC3F, and APOBEC3G, without the induction of signals that lead to their maturation (93),(97),(98). Unlike macrophages, HIV-1 DNA in myeloid DCs is hypermutated upon IFN-a treatment; transmission from myeloid DCs to T cells is significantly reduced compared with IFN-naive cells (97). B cell expression of APOBEC3G is higher than that seen in monocytes (42). nevertheless, because B cells lack the entry receptors required for HIV-1 infection, APOBEC3G is unlikely to play a role in cell-intrinsic restriction (99). APOBEC3G was shown to be a major exosomal component, and exosomes bearing APOBEC3G can confer anti–HIV-1 activity to Jurkat T cells (100). APOBEC3G levels are up-regulated upon treatment of B cells with a combination of agonists, such as CD40L, IL-4, and anti–HLA class II Abs, and autologous CD4+ T cells co-cultured with B cells activated with these agonists are significantly less infected by HIV-1 (101). APOBEC3G derived from exosomes produced by activated B cells confers antiviral activity to CD4+ T cells (101). B cell– expressed APOBEC3 proteins may also act on other viruses that infect this cell type, such as EBV (102).

6. APOBEC3 and the innate immune response

APOBEC3 genes are IFN-stimulated genes (ISGs) whose expression is increased in response to various stimuli, including the ligands of TLR3, TLR4, and TLR7 (97),(98),(103),(104),(105), (106),(107),(108). Thus, the activation of innate immune responses that occurs upon infection with many viruses could lead to increased APOBEC3 activity. Expression of IFNs and other cytokines/chemokines is induced by virus infection, the result, in part, of cytosolic nucleic acid sensors that detect single- and double-stranded RNA and DNA (109). Studies showed that reverse transcribed retroviral DNA is recognized by several sensors, including cyclic GMP-

AMP synthase and members of the absent in melanoma 2 (AIM2)-like receptor family that subse-quently signal through the stimulator of IFN genes (STING) pathway (110),(111),(112). As described above, APOBEC3 proteins inhibit reverse transcription in addition to introducing CDA-induced mutations. Thus, APOBEC3-mediated inhibition of reverse transcription would seemingly limit cytosolic sensing and the IFN-induced antiviral response. Indeed, we showed recently that, in mice, APOBEC3 in macrophages limits the levels of retroviral reverse transcripts that trigger cytosolic sensing (112). However, reverse transcripts that escaped this blockade activated the STING pathway via cytosolic sensing and induced type 1 IFN expression. This, in turn, increased expression of ISGs like APOBEC3, reducing virus loads in vivo. Because human APOBEC3 proteins also block reverse transcription in sentinel cells and lentivirus reverse transcripts trigger STING via cytosolic sensing, it is likely that similar interactions between the two restriction pathways occur during HIV infection. Interestingly, DNA viruses, like herpes viruses, also induce IFN production via the cytosolic sensor–STING pathway and would be predicted to induce antiviral APOBEC3 expression that could then act on these viruses. APOBEC3G also was linked to increased destruction of HIV-1–infected cells by NK cells (113). Cells infected with HIV lacking or encoding defective Vifs unable to bind APOBEC3G have higher levels of the NKG2D ligands, such as ULBPs and PLAP, resulting in more efficient NK cell–mediated lysis. The increase in lysis was linked to higher uracil content in HIV reverse transcripts caused by APOBEC3G-mediated cytidine deamination. Uracils are removed from DNA via cleavage by uracil–DNA glycosylase, which then activates the base excision– repair pathway.

7. APOBEC3 and the adaptive immune response

Clearly, APOBEC3 proteins play a role in the intrinsic/innate response to, and the subsequent control of, early virus infection. There is increasing evidence that APOBEC3 proteins also contribute to the adaptive immune response by affecting the generation of CTLs that recognize viral peptides and perhaps B cell production of antiviral Abs. Because APOBEC3 expression is induced by virus infection of APCs, as discussed above, this may afford additional layers of host protection. HIV may take advantage of nonlethal mutations induced by APOBEC3 proteins to generate such CTL escape variants (114), APOBEC3G/F hotspots in the HIV genome are enriched in immunogenic CTL epitopes, and deamination at these hotspots diminished CD8+ T cell responses to infected cells (115),(116). In contrast, the host may strengthen its intrinsic ability to control HIV-1 infection by selecting for immune escape variants; there are known CD8 epitopes in Vif itself and Vif immune escape variants would be predicted to more weakly counteract APOBEC3s (117),(118). Indeed, the virus-specific CTL response to APOBEC3G-expressing, HIV-infected APCs is increased compared with APCs that do not express the CDA (119). Moreover, the activation of HIV specific CTLs was stronger with vif-deficient HIV-infected APCs. However, a recent report that longitudinally followed pol and env sequences in a large cohort of patients chronically infected with HIV-1 found that the vast majority of the G-to-A mutations fell into the recognition motif for APOBEC3F and the other APOBEC3 proteins and not that of APOBEC3G (115). Indeed, for many viruses, including HIV-1, there is an inverse correlation between CTL response and viremia and disease progression (120),(121). Thus, the effects of APOBEC3 proteins on the CTL response can have a significant impact on retrovirus infection and evolution. B cell production of virus-neutralizing Abs may also be altered by APOBEC3 proteins. APOBEC3-knockout mice generate neutralizing Abs against Friend murine leukemia virus (FV) with significantly slower kinetics compared with wild type mice, although

the responses in APOBEC3-knockout mice eventually become as high as those in wild-type animals (122). This effect on the antiviral humoral immune response is likely due to APOBEC3-mediated suppression of virus infection at early times, thereby limiting the number of virus-producing cells in the early stages of infection. This may reduce Ag load and the induction of immune tolerance or prevent FV-mediated damage of critical hematopoietic lineage cells required for generating an immune response (122),(123). APOBEC3 may also play a role in somatic hyper mutation of Abs. AID is the primary CDA involved in somatic hypermutation of Ig genes that results in the diverse repertoire of Abs needed to clear infections (124). Nevertheless, because the human APOBEC3 proteins APOBEC3A and APOBEC3B have been implicated in mutating genomic DNA, it is possible that they contribute to the development of neutralizing Abs during virus infection (125),(126).

8. Inhibition of Cytoplasmic Defenses: Vif

The HIV-1 Vif protein (virion infectivity factor) is 192 amino acid cytoplasmic protein whose essential role in replication in primary T cells and during natural infection has long been established. Though certain cultured cell lines are able to support growth of vif-deficient viruses, cell fusion experiments indicated that such cells lack expression of inhibitory factor(s) that naturally block viral replication when Vif is absent. By comparing mRNA expression profiles in cells where Vif is, or is not, required for HIV-1 replication, the human gene APOBEC3G (A3G) was identified as being fully sufficient to prevent productive infection in the absence of Vif (127). Specifically, A3G is a member of the APOBEC family of editing enzymes, many of which can mutate polynucleotides by deaminating cytidine (C) to uridine (U) (128),(129),(130). Indeed, in the absence of Vif, newly synthesized A3G is packaged into budding viral particles through a combination of A3G-RNA and A3G-Gag interactions (131),(132), and consequently carried forward to newly infected cells where it deaminates C residues to U residues in nascent minus (first) strand reverse transcripts (128),(129),(130). Indeed, evidence from examining the fossil record of endogenous retroviruses in the genome of mice and humans indicates that some ''ancient'' retroviral infections were inactivated by APOBEC3- mediated mutations (133). In the majority of wild-type viral infections, Vif effectively antagonizes the antiviral effects of A3G through the recruitment of a cullin-RING ubiquitin ligase and the induction of polyubiquitylation (of A3G and Vif itself) and degradation (55),(134). In the case of A3G, Vif simultaneously binds to a specific region of A3G centered around an aspartic acid residue at position 128, as well as to the elonginC and cullin5 components of the cullin5-elonginB/C complex, via its BC box (a peptide motif that binds elonginB/C) and a zinc coordinating motif, respectively(135),(136), (137). By eliminating A3G from virus-producing cells, and perhaps by impeding packaging via a more direct mechanism, Vif therefore allows progeny particles to be produced that are free of A3G. Interestingly, phosphorylation of a conserved serine in Vif's BC box inhibits binding to elonginC (55), suggesting that the degradation of A3G in infected cells may also be regulated by signaling pathways that have yet to be explored in detail ((138), Vif function is also species specific. Vif proteins from HIVs and SIVs whose ancestors have established infections in humans efficiently inhibit human-A3G, whereas Vifs from SIVs whose ancestors have not been transmitted to humans do not (139). For A3G, the molecular basis for specificity corresponds to Vif binding (130). For example, HIV-1 Vif binds human-A3G but not A3G from AGMs; conversely, SIV-AGM Vif binds AGM-A3G but not human A3G. Thus, the ability to overcome the APOBEC proteins of a recipient species correlates with transmission potential, thus marking Vif as an

important determinant of lentivirus transmission. Importantly, A3G is only one of a set of seven cytidine deaminase genes encoded by a locus on human chromosome 22 (APOBEC3A-H), and the anti-HIV-1 phenotypes of these other APOBEC proteins have been extensively cataloged using cultured cell assays (130). In sum, A3G has the most potent inhibitory effect and A3F is also very active, while A3B is much less so. Of these, A3B is not regulated by Vif and is barely expressed in T cells, which suggests a lack of relevance in vivo for HIV-1 infections. A3F, like A3G, is also linked to the cullin5-elonginB/C ligase by Vif and correspondingly degraded (140)). Interestingly, mutations have been described in Vif that segregate the ability to down-regulate A3G versus A3F (141),(142),(143). implying that the adaptation of HIV-1 to humans necessitated that Vif maintain at least two distinguishable APOBEC3 binding interfaces. Specifically, analyses of HIV-1 sequences from infected persons frequently reveal subsets of sequences that are distinguished by excessive G-to-A hypermutation (144). The local nucleotide sequence preferences for such mutations have been calculated and match those determined for A3G (predominantly) and A3F in transfection based experiments (130). Suggesting that these APOBEC proteins are the most significant for driving HIV-1 hyper-mutation in vivo Presumably, such sequences arise when A3G/F occasionally escape Vif-mediated inhibition. and become encapsidated into viral particles. Hypermutation, while clearly central to the profound impact of A3G on HIV-1 infection, is not the only mechanism through which antiviral effects are exerted. First, and noted originally by examining deaminase-deficient proteins, infectivity can be reduced in the absence of DNA editing (145). While not yet entirely explained at the molecular level, these effects are associated with diminished reverse transcription (130),(146),(147). Second, and perhaps mechanistically related, A3G residing in target cells (i.e., not present in virions) has been reported to impede the synthesis of viral DNA by incoming viral particles in quiescent T cells without inducing hypermutation (148). Different retroviruses have adopted different strategies to evade suppression by APOBEC proteins. Human T cell leukemia virus type 1, like HIV-1, replicates in CD4 T cells but averts significant inhibition by not packaging A3G into virions through the action of sequences in the nucleocapsid (NC) region of Gag, thus avoiding the need for a Vif-like factor (149). Because a regulatory interaction has the potential to be variable in its extent, sporadic partial inhibition of A3G/F by Vif (e.g., through variation in either A3G/F expression or Vif sequences (142), may allow sufficient levels of these proteins to survive and confer low levels of editing. Population level studies of HIV-1 infected cohorts also support the notion that the balance between APOBEC proteins and their downregulation by Vif is dynamic and subject to variation: specifically, there is evidence that genetic polymorphisms in A3G or cullin5 are associated with differences in the rates of disease progression (150). As potential DNA mutagens, especially those that accumulate in the nucleus (A3A, A3B, and A3C), it seems intuitive that APOBEC3 protein function would be negatively regulated in some manner in the absence of viral infection to protect against deleterious mutation of cellular genomic DNA. Among A3G's (and A3F's) interactions with cellular proteins, those with the Argonaute proteins, the effector components of RNA-induced silencing complexes, are notable (151),(152). Whether APOBEC proteins are therefore able to modulate RNA silencing pathways and translational regulation (153), and what possible connections there may be to cellular function and/or HIV-1 replication, remains largely unexplored (readers should refer to the accompanying Review by Gottwein and Cullen on page 375 that discusses interactions between viruses, microRNAs, and RNA silencing). Moreover, comparisons among the A3G sequences of a large panel of diverse primates revealed that these genes have been subject to nearly constant severe positive selection throughout the past 33 million years of primate evolution (154), and comparison of the entire cluster of APOBEC3 genes indicates that

most of them have rapidly evolved since human-chimpanzee speciation (154). Since many retroviruses and retrotransposons, as well as hepatitis B virus, can be inhibited by APOBEC3 family members (130). and the human genome contains active LINE-1 and Alu elements, it is likely that the APOBEC3 genes have evolved to defend against genomic assaults by a broad spectrum of retrovirus-like parasites. Recent results showing that two very different DNA viruses, adeno-associated virus and human papillomavirus, can be inhibited or subjected to G-to-A editing, respectively, by APOBEC3 proteins reveals that the range of substrates for these enzymes extends beyond those requiring reverse transcription (155),(156).

9. Vif Antagonize SAPOBEC3G

As described above, the main function of Vif is to antagonize APOBEC3G. Right after identification of APOBEC3G, many studies have shown that Vif inhibits the virion in corporation of APOBEC3G, which is mainly attribute able to degradation of cellular APOBEC3G via the proteasomal pathway(157),(127),(55). How- ever, some studies have also shown that Vif directly inhibits the virion in corporation of APOBEC3G(158), or thatVif inhibits translation of APOBEC3G (159),(160). Vif also antagonizes other APOBEC3 proteins From APOBEC3C to H by the same E3 ligase complex (161). Virion infectivity factor binds to the E3 ligase complex through Two interactions ites; it binds to E long in C through its sup-pressors of cytokine signaling (SOCS) box motif (55), S144LQYLA149, and to Cullin 5 through a zinc-binding motif (162),(163), H108x5Cx17−18Cx3−5H139. The SOCS box motifis well Conserved among Vif proteins, indicating that this motifis crucial for Vif function, and mutation of S144, apresumed phosphorylation siteinVif, affects binding of Vif to E longin C (55). The zinc-binding motifis also important for Vif function To form the E3 ligase complex. Therefore, azinc chelating agent can inhibit Vif function in infectivity assays (164).

10. The Interaction OF Vif with APOBEC3 Proteins

It is quite important to reveal the interaction sites between Vif and APOBEC3 proteins, because the regulation of this interaction may lead to the development to novel therapeutic strategies for HIV-1infection. The most important and confirmed evidence is that the interaction between Vif and APOBEC3G is critically dependent on D128PD130 in APOBEC3G (135). Many groups have simultaneously reported this evidence by comparing human and African green monkey (agm) APOBEC3G (165),(166),(24),(167). In detail, HIV-1 Vif binds and antagonizes human APOBEC3G, but notagm APOBEC3G.In contrast, SIV agm Vif antagonizes agm APOBEC3G, but not human APOBEC3G. By comparing amino acids residues and preparing chimeric APOBEC3G between human and agmAPOBEC3G, they identified D128 as the determinant of the species-specific binding of Vif to APOBEC3G (165),(166),(24),(167). On the other hand, SIV mac and HIV2 Vif can antagonize both human and agmAPOBEC3G, indicating that the interaction between Vif and APOBEC3G is not restricted by D128, in other words, D128 is not the sole determinant for species-specific target by Vif (168). Furthermore, the interaction between Vif and APOBEC3G is regulated by phosphorylation of APOBEC3G at T32 by proteinkinase A (169). The interaction sites in Vif are reported by many groups and are much more complicated. The binding site only for APOBEC3G isY40RHHY44 (141),), while that only forAPOBEC3FisD14RMR17 (141), and T74GERx W79 (170). The binding sites for both APOBEC3G and Fare W21KSLVK26 (171),(172). V55xIPLx4−5LxΦx2YWxL72 (170),

11. The Vif-A3G Interaction

Recent advances on the biological role of HIV-1 Vif and A3 proteins, together with progress in deciphering how Vif counteracts A3G and A3F opened new opportunities to develop anti-HIV drugs. However, understanding the mode of action of Vif and A3G alone can provide a number of attractive targets for drug development since A3G displays the most potent activity against HIV-1. Disruption of Vif-A3G interaction is predicted to rescue A3G expression and virion packaging, consequently stimulating intracellular antiviral activity. Similarly, pharmacologic studies to suppress A3G proteasome-mediated degradation have been shown to enhance A3G half -life and consequently inhibit HIV-1 infection (13). In order to facilitate the rational design of inhibitors for Vif-A3G interaction, experimental assays have been devised to define features of Vif that are involved in the interaction with A3G, and vice versa. The N-terminal region of HIV-1 Vif is important for binding and neutralization of A3G and A3F and also contributes to species-specific recognition (33),(173),(174),(175). In the C-terminal region of Vif, the highly conserved cysteine residues at positions 114 and 133 and the S144LQXLA149 motif are required for Vif function and HIV-1 replication (50),(176). Vif associates with the Cul5-EloB-EloC complex by directly binding to EloC via a BC box motif at positions 144 to 150 and to Cul5 via hydrophobic residues at positions 120, 123, and 124 within a zinc-binding region formed by the highly conserved HCCH motif (55),(136). The SLQXLA motif is essential for targeting A3G for proteasomal degradation. Substitution of the SLQ portion of the SLQXLA motif has been reported to be sufficient to prevent A3G degradation (69),(13),(177). The zinc binding motif HCCH is also involved in A3G degradation and necessary for the specificity of Vif-Cul5 interaction (178),(179). Several groups have shown that Vif-induced degradation of A3G requires the physical interaction of the two proteins and that a single amino acid change in A3G at residue 128 was sufficient to abolish this interaction (180),(181),(24). This assumption led to the conclusion that the Vif-A3G interaction is species-specific and is determined by aspartic acid at position 128 in A3G and lysine in African Green Monkey (AGM) (180),(181),(24). Experiments using alanine-scanning and multiple synonym substitutions on A3G residues confirmed the central role played by the aspartic acid at position 128 and showed the crucial role of proline-129 and aspartic acid-130, as important contributory residues (135). Specifically, resistance to Vif induced degradation was conferred by mutating the aspartic acid residue at position 128 or 130 to the positively charged residue lysine, indicating that the interaction between Vif and A3G is largely determined by electrostatic interactions involving these residues (135). However, residue 128 has been shown to be more sensitive to amino acid alterations than 130, suggesting that amino acid D128 may play a more prominent role in A3G interaction with Vif (135). Substitution of proline in residue 129 of A3G to alanine or glycine displayed a strong Vif-resistant phenotype indicating that a specific structural interaction is also required for an efficient inhibition of A3G by Vif (135). In addition to electrostatic determinants, one study reported that A3G residues 54−124 were sufficient to coimmuno precipitate Vif, suggesting the role of additional interacting domains between Vif and A3G (182). Recently, analysis of A3G chimeras identified amino acids 126−132 as critical determinants involved in Vif interaction (Figure 1(b)) (183). Finally, by using model-guided mutagenesis, four Lys residues in the CDA of A3G (Lys-297, 301, 303, and 334) were recently identified as required for Vif-mediated polyubiquitination and degradation (184). Asparagine at position 128 of A3G was shown to interact with amino acids 15 or 17 of Vif, and mutations in the D14RMR17 conserved region of Vif can also alter its speciesspecific effect (174). Alteration of DRMR region to SERQ or SEMQ, which are present in SIVAGM Vif, promotes the interaction of AGM A3G, rhesus (Rh) A3G, and

D128KA3G with HIV-1 Vif (174). The loss of species restriction is probably caused by an overall increase in the negative charge of amino acids in the 14−17 region of HIV-1 Vif, which promotes effective interaction with the positive charge of lysine present at residue 128 in AGM A3G and Rh A3G. In addition, the DRMR region was also shown to be critical for the binding strength between A3G and Vif although, additional interaction motifs were required for stabilization of this interaction (141). Vif Y40RHHY44 motif was considered a critical domain for binding to A3G while the D14RMR17 domain could be involved in a secondary step involving A3G degradation (141). Nonetheless, other amino acids in Vif may also contribute to A3G binding. Mehle et al. demonstrated that amino acids 40 to 71 in the N-terminus of Vif contain a nonlinear binding site for A3G and that His 42/43 are important for Vif-A3G binding and Vif-mediated degradation of A3G in vivo (185). Recently, a highly conserved 69YXXL72 motif in Vif was shown to mediate the binding to human A3G and its subsequent degradation (Figure 1(a)) (170),(186),(187). Pery et al. showed that this motif was critical for in vitro direct binding of recombinant GST-Vif (1−94 a.a) to A3G and by FRET assay (186). Additionally, Vif residues 22−26 and Y30 were also involved in the interaction with APOBEC3 proteins(171). (172). In particular, Vif K22 and K26 were shown to be important for degradation of A3G. Additionally, residue Y30 was involved in the interaction with both A3G and A3F raising the hypothesis that alteration of Tyr in position 30 may affect the conformational stability of Vif.. Vif-mediated degradation of A3G is regulated by phosphorylation of Vif and A3G at Ser144 and Thr32, respectively (169). It was recently documented that phosphorylation of A3G by protein kinase A (PKA) reduces its binding to Vif affecting subsequent ubiquitination and degradation (169). This finding indicates that phosphorylation events may also play an important role in the interaction between Vif and APOBEC3 proteins. The central hydrophilic domain, E88WRKKR93, and the proline-rich P161PLP164 domain of Vif have been implicated in enhancing its steady-state level and in binding to tyrosine kinases, respectively (188),(189). It is conceivable that the E88WRKKR93 motif is involved in maintaining sufficient intracellular levels of Vif necessary for A3G inhibition. Mutations in the PPLP motif of Vif were shown to reduce the infectivity of virions produced in T cells and inhibit Vif-Vif interaction in vitro (52).

12. A Novel Vif Function: G2 Cell Cycle arrest

recent reports came out, describing that Vif as well as Vpr- induce G2 arrest in HIV-1-infected cells (190),(191). We have recently shown the molecular mechanisms by whichVif induces G2 arrest (192). Vif activates p53,which is well known as a tumor suppressor gene and the regulator of cell cycle as“a guardian of the genome.” Vif binds and activates p53 by stabilizing and sequestering it to the nucleus. Activation of p53 induces its downstream cascade such as activation of p21 and inactivation of Cdc2/ Cyclin B, resulting in G2 arrest. Using amutant virus which possesses the *vif* mutant, we have demonstrated that Vif- induced G2 arrest facilitates viral replication(192). Thus,HIV-1 needs to have G2 cell cycle arrest to efficiently replicates o that it possesses two accessory genes such as *vif* and *vpr*. Vif induces G2 arrestina p53-dependent manner, while Vpr accomplishes the same goalina p53-independent manner.

13. Vif protein–protein interactions are sites for therapeutic targeting

Vif likely forms at least seven potentially druggable interfaces including that with CBFb, EloC, Cul5, itself (dimerization domain), and the APOBECs (A3D, F, G, and H). Although disrupting any of these protein–protein interactions in-volving Vif or any of the other interactions in the

context of the E3 ubiquitin ligase would theoretically abrogate A3 degradation, the most prudent approach is to target Vif directly to avoid unwanted off-target interactions that may lead to cytotoxicity. Specifically, disrupting interaction of Vif with CBFb could unleash the natural host antiretroviral activity of each of the A3 proteins simultaneously, while mitigating the potential for nonspecific target effects on other cellular SOCS-box type E3 ubiquitin ligase complexes that function as a part of normal cell metabolism.. In addition, CBFb is not believed to be a component of cellular E3 ubiquitin ligase complexes, making its interac-tion with Vif unique. The interaction between Vif and CBFb is large (4800 A °2 of surface area is buried at the interface). Disruption of this interaction by a drug-like molecule that is smaller than the suggested upper size limit (500 Da) (193), may seem insurmountable. However, recent evidence suggests that much of the free energy of binding is confined to smaller sections of interacting protein surfaces, deemed 'hotspots', thus negating the notion that such a large PPI is undruggable. It is becoming clear that Vif may interact with A3 proteins (D, F, G, and H) through unique and different interfaces. Thus, the Vif interaction with each A3 protein may have to be targeted separately. We suggest targeting interaction of Vif with A3G as a top priority because A3G has the most potent antiretroviral activity. Therapeutic inhibition of Vif-mediated degradation of A3G may facilitate A3G incorporation into budding virions and subsequent A3Gmediated lethal mutagenesis of the HIV-1 single-stranded DNA during reverse transcription. Likewise, targeting disruption of Vif oligomerization could potentiate the antiretroviral activity of A3s. Conversely, targeting interaction of Vif with either Cul5 or EloC directly, while still preventing A3 degradation, would have a higher risk for off-target interactions and perhaps cytotoxic effects. The BC-box backbone from HIV-1 Vif and cellular SOCS-box proteins are nearly isomorphous, suggesting that therapeutic intervention targeting disruption of the Vif–EloC interface could also disrupt the interaction between cellular SOCS-box proteins and EloC. Thus, the Vif–EloC interface is a more tenuous and lower-priority target for small molecule disruption. In conclusion, we consider targeting interactions of Vif with CBFb, A3G, and itself (oligomerization) top priorities for developing a new class of antiretroviral therapeutics.

14. Conclusion Remarks

Understanding the mechanisms by which the virus is able to successfully replicate in host cells and subsequently cause gradual destruction of the immune system may yield new approaches for therapeutic strategies. APOBEC3 proteins have clear roles in conferring intrinsic host resistance to infection to different viruses as a result of their ability to directly act on viral genomes, thereby generating mutations or blocking viral nucleic acid synthesis. There is also a body of evidence that APOBEC3 deaminase activity plays additional antiviral roles in innate and adaptive immunity. Whether these additional mechanisms operate in the antiviral response to other virus families remains to be determined. Recent advances in the study of the biological and biochemical role of Vif and A3G, together with progress in deciphering how Vif counteracts A3G, opened new opportunities to develop novel anti-HIV drugs. Blocking the binding of Vif to A3G *in vivo* is certainly one of the most obvious therapeutic strategies. Several study reported that Vif may function at multiple levels to prevent incorporation of A3G into viral particles (194),(160),(31),(158). Therefore, preventing the binding of Vif to A3G may have two outcomes: (1) inhibition of A3G proteasomal degradation and, (2) increasing in the amount of A3G at viral

assembly locations, resulting in a higher level of A3G incorporation into virions..The amount of intracellular Vif can be reduced by degradation in the proteasome due to direct interaction with the SCF complex. Consequently, disruption of Vif-A3G interaction could prevent the proteolytic degradation of A3G and consequently increase the intracellular levels of Vif by impeding its destruction. Thus, chemical compounds targeting this region could be effective in preventing Vif- A3G interaction. The Vif protein is also a potential target for HIV-1 drug therapy. In contrast to A3G, Vif has a scattered localization of motifs capable to mediate its interaction with APOBEC3 proteins. The N-terminal region of Vif has been implicated in binding to A3G, whereas the protein motifs that mediate interaction with Cul5-E3 ligase complex and promote A3G degradation are concentrated in the C-terminal region of Vif Interestingly, when an anti-viral peptide that mimics the Vif PPLP dimerization domain was used, the amount of A3G incorporation into wild-type HIV-1 particles increased (195). Thus, small molecules that target this motif could be developed as antiviral drugs to block the Vif-mediated inhibition of A3G and A3F activity (195). Using molecular dynamics simulation, it was shown that mutations of criticalNresidues led to the disruption of Vif and EloB-EloC interaction, consistent with experimental observations. These novel homology models of Vif can therefore provide structural information for investigating critical domains for protein neutralization (196),(197), (198),(199),(200). Nonetheless, developing specific and effective small chemical inhibitors to directly inhibit Vif-A3G interaction faces many challenges due to the multiple binding regions involved. In addition, *in vitro* binding assays and cell-based assays that have been used to decipher the dynamic principles behind protein functional association make it sometimes difficult to assess the *in vivo* significance of the results (201). It is believable that the binding features of Vif-EloC interaction present mechanistic specificities that would be optimal for the rational development of a Vif antagonist (202),(132). The interaction interface between the N-terminus of Vif and CBFβ and identified a tripartite interaction that plays a major role in Vif–CBFβ binding. Together with the available structural data on Vif–CBFβ–E3 ubiquitin ligase complex, these results further our understanding of the biology of HIV-1 Vif–CBFβ interaction and may aid in the development of novel therapeutics that target the Vif–CBFβ interaction and inhibit Vif-mediated degradation of A3 proteins. In conclusion, antiviral drugs and broad neutralizing antibody that could inhibit Vif and enhance A3G/A3F activity and inhibit Vif-mediated degradation of A3 proteins are emerging as attractive candidates (196),(197),(198), (199). Nevertheless, the potential outcome of a Vif-based intervention must be examined rigorously both *in vitro* and *in vivo* prior to clinical deployment.

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