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APOBEC3 family proteins as drivers of virus evolution

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The apolipoprotein B mRNA editing enzyme catalytic polypeptide-like (APOBEC) family consists of cytosine deaminases implicated in diverse and important biological functions. APOBEC3 (A3) proteins belong to the APOBEC/AID family, and they catalyze the deamination of cytosine to uracil in single-stranded DNA and, to a lesser extent, in RNA substrates. In humans, seven *A3* genes have been identified (*A3A*, *A3B*, *A3C*, *A3D*, *A3F*, *A3G*, and *A3H*). The introduction of lethal G-to-A or C-to-U mutations into certain viral genomes leads to virus inactivation. However, the mutagenic capability of A3 proteins could serve as a source of mutations to drive virus evolution. Therefore, recent studies have implied the role of A3 proteins in aiding the evolution of viruses, conferring them with severe manifestations such as drug resistance and/or immune evasion. In this review, we discuss in depth the interactions of A3 proteins with viruses that infect humans and our self-proteins.

KEYWORDS

APOBEC3, C-to-U/G-to-A mutations, deamination, retroviruses, DNA viruses, RNA viruses, virus evolution

1 Introduction

The apolipoprotein B mRNA editing enzyme catalytic polypeptide-like (APOBEC) family comprises cytosine deaminases implicated in diverse and important biological functions. The first member of this group to be characterized was APOBEC1 (A1) (1, 2), which participates in lipid metabolism through the editing of *apolipoprotein B* mRNA [reviewed in (3–6)]. Later, several A1 proteins in nonhuman species were demonstrated to deaminate single-stranded DNA (ssDNA) (7–9) and exhibit potential to inhibit retroviruses, including human immunodeficiency virus type I (HIV-1), in cell line models (9–13). The second member of this family to be identified was activation-induced cytosine deaminase (AID) (14), known for its importance in the antibody diversification of immunoglobulin genes and class switch recombination [reviewed in (6, 15, 16)]. Other members of this group including APOBEC2 (A2) (17) and APOBEC4 (A4) (18) are less characterized [reviewed in (6)].

APOBEC3 (A3) proteins belong to the APOBEC/AID family. These proteins catalyze the deamination of cytosine to uracil in ssDNA substrates [reviewed in (19–21)]. In humans, seven *A3* genes (*A3A*, *A3B*, *A3C*, *A3D*, *A3F*, *A3G*, and *A3H*) are tandemly arranged into a gene cluster between the flanking genes *CBX6* and *CBX7* on chromosome 22 [reviewed in (19, 22, 23)] (Figure 1A). *A3* genes are the products of arduous evolution over 100 million years (24). The deaminase activity of A3 proteins is attributable to the presence of a conserved zinc-binding motif (Z domain). A3A, A3C, and A3H proteins have a single Z domain, whereas A3B, A3D, A3F, and A3G proteins have double Z domains [reviewed in (19–21, 23, 25)] (Figure 1A). The mechanism of A3 protein-mediated catalysis involves a zinc-mediated hydrolytic reaction (Figure 1B). Histidine and cysteine residues are responsible for the coordination of the zinc ion required for the catalytic activity of these proteins, whereas a glutamate residue facilitates the removal of the amine group from the substrate deoxycytidine [reviewed in (26–28)] (Figure 1B). First, a glutamic acid residue in the Z domain deprotonates water and forms a zinc-stabilized hydroxide ion (Figure 1B). Second, the third nitrogen atom (N3) of the cytosine pyrimidine ring is protonated, leading to the disturbance of a double bond between N3 and the fourth carbon atom (C4) of the cytosine pyrimidine ring (Figure 1B). Third, this causes the zinc-stabilized hydroxide ion to attack C4, forming a double bond and essentially converting cytosine into uracil [reviewed in (26–28)] (Figure 1B). The differences among the A3 proteins also extend to their nucleic acid sequences. The stretch of nucleotides recognized by A3 proteins can be grouped into two types, namely 5′-CC and 5′-TC (the target cytosines are underlined; see Figure 2). The former is recognized by A3G protein, whereas the latter is preferred by other A3 proteins (12, 29–35).

Interestingly, because of their RNA-binding capacity, most A3 proteins are incorporated into ribonucleoprotein complexes in cells immediately after translation. Multiple reports have documented that A3G protein can form higher-order, high molecular mass ribonucleoprotein (HMM RNP) complexes composed of A3G-binding RNAs, A3G-binding proteins, and numerous cellular RNA-binding proteins (36–47). Similarly, the ability to form HMM RNP complexes is conserved in other A3 members (at least in A3B, A3C, A3F, and stable A3H proteins, but not A3A protein) (39, 44, 48, 49). Importantly, this capability inactivates the catalytic activity of A3B, A3G, and A3H proteins, as RNase treatment can restore their enzymatic activity by abrogating HMM complex formation, leading to a shift toward low molecular mass (LMM) complexes (40, 49–52). The shift toward LMM complex formation allows the A3G protein to be packaged into nascent virions for anti-HIV-1 activity (40). Therefore, the formation of A3 HMM RNP complexes (with the exception of A3A) is one of the regulatory mechanisms for the mutagenic activity of A3 proteins, and A3 enzymatic activity is altered by cytokines such as interferons (IFNs) and different cell types (41, 46, 47, 53). Furthermore, differences in each A3 interactor potentially lead to differences in the localization of A3 proteins in cells. A3A and A3C proteins are distributed throughout the cell, whereas A3B protein is localized exclusively to the nucleus (30, 51, 54–62). Notably, endogenous A3A protein in $CD14^{+}$ primary cells and IFN-stimulated THP-1 cells is localized to the cytoplasm, which is distinct from the overexpressed A3A protein in HEK293 cells (56). This distinct subcellular localization pattern of overexpressed and endogenous A3A protein suggests the existence of regulatory mechanisms for A3A activity and/or provides a potential explanation for its genotoxicity. Meanwhile, A3D, A3F, and A3G proteins are exclusively localized in the cytoplasm (30, 36, 44, 54, 55, 57, 59–61). However, A3G protein was recently reported to localize to the nucleus of bladder cancer cells *in vivo* (63) and in human T cell lines in small amounts (64, 65). Interestingly, A3H protein has a haplotype-dependent localization in cells: haplotype I is distributed through the cell (55, 66) and haplotype II is present in only distinct subcellular

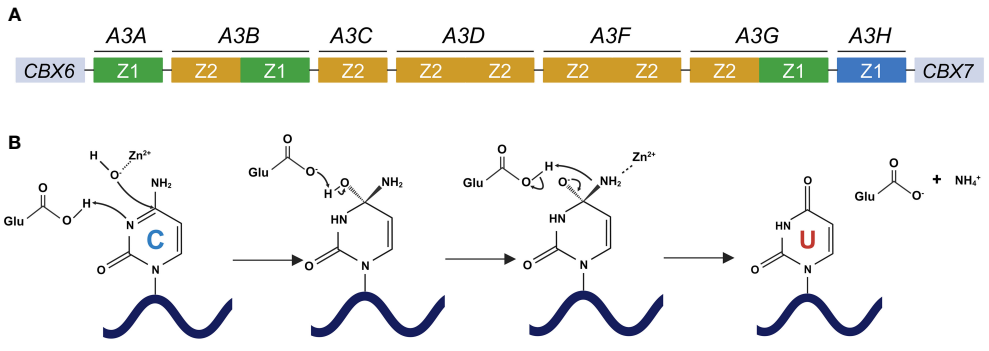

FIGURE 1
Human *A3* gene organization and deamination catalyzed by A3 proteins. **(A)** Human *A3* genes are arranged tandemly between *CBX6* and *CBX7* on chromosome 22. A3 family proteins include single or double deaminases, which are composed of three phylogenetically different groups, namely Z1 (green), Z2 (orange), and Z3 (blue) domains. **(B)** The deamination process by which cytosine is converted to uracil by A3 proteins. A glutamic acid residue in the Z domain of A3 proteins deprotonates water and forms a zinc-stabilized hydroxide ion. The third nitrogen atom (N3) of the cytosine pyrimidine ring is protonated, thereby disturbing the double bond between N3 and the fourth carbon atom (C4) of the cytosine pyrimidine ring. This causes the zinc-stabilized hydroxide ion to attack C4, forming a double bond and essentially converting cytosine into uracil. *CBX6*, chromobox 6; *CBX7*, chromobox 7; *APOBEC3/A3, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3*; *A3A, APOBEC3A; A3B, APOBEC3B; A3C, APOBEC3C; A3D, APOBEC3D; A3F, APOBEC3F; A3G, APOBEC3G; A3H, APOBEC3H*. Created with BioRender.com.

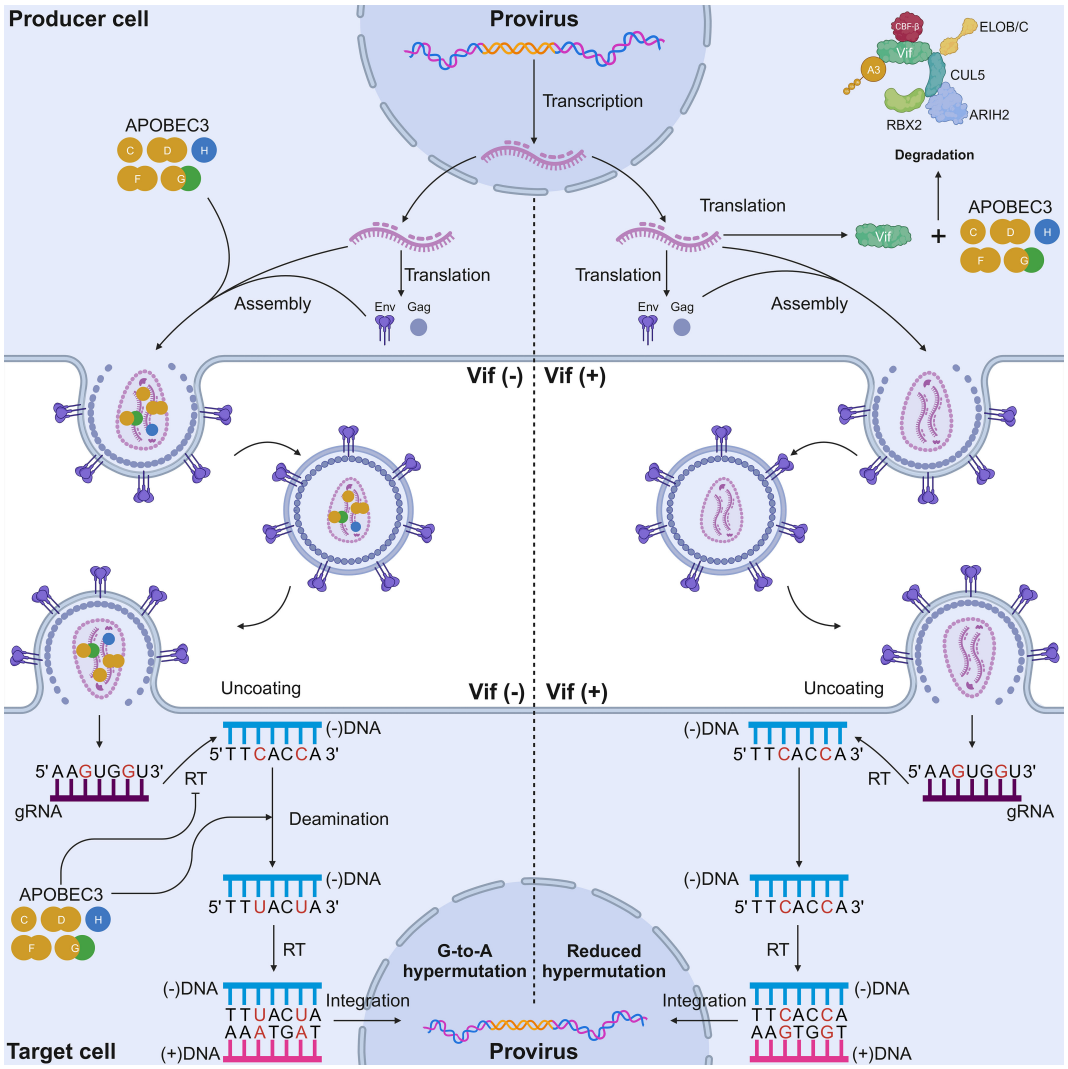

FIGURE 2
Mechanisms of HIV-1 inhibition by A3 proteins and the counteraction of Vif. In a Vif-deficient virus infection scenario (left), the lack of Vif causes A3 proteins to be packaged into nascent virions. A G-to-A mutation occurs in the single-stranded cDNA intermediate of HIV-1, resulting in deleterious and potentially lethal mutations. A3 proteins have different dinucleotide motifs. A3G prefers 5′-CC-3′ motifs, whereas the other six A3 proteins prefer 5′-TC-3′ motifs (target cytosines are presented in red). A3 proteins also physically inhibit reverse transcription via their deaminase-independent activity to prevent HIV replication. In a Vif-proficient virus infection scenario (right), Vif ubiquitinates A3 proteins for degradation. None or a reduced number of A3 proteins is packaged into nascent virions. Sublethal levels of A3-mediated mutagenesis can occur in the single-stranded cDNA intermediate of HIV-1. RBX2, RING box protein 2; ARIH2, ariadne RBR E3 ubiquitin protein ligase 2; CBF-β, core-binding factor subunit beta; ELOB, elongin B; ELOC, elongin C; Vif, viral infectivity factor; CUL5, cullin-5; A3, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3; RT, reverse transcriptase; Env, envelope; Gag, group-specific antigen. Created with BioRender.com.

compartments, namely the cytoplasm and nucleolus (30, 50, 66, 67). The distinct subcellular localization of A3H haplotypes may be a regulatory mechanism for the antiviral activity of this protein.

2 A3 proteins as innate antiviral restriction factors

Much of the knowledge about the function of A3 proteins as restriction factors stemmed from studies of retroviruses, with HIV-1 being the most well-documented retrovirus [reviewed in (19–21, 68–70)]. Initially, A3G was identified as a specific inhibitor of viral infectivity factor (Vif)-deficient HIV-1 (71). Thereafter, it was elucidated that this antiviral protein is packaged in nascent virions in virus-producing cells, and it triggers the lethal deamination of cytosine to uracil in the HIV-1 minus-strand cDNA intermediate in target cells (71–73) (Figure 2). Currently, up to five A3 proteins (A3C-I188, A3D, A3F, A3G, and stable A3H haplotypes) contribute to HIV-1 restriction in human $CD4^+$ T cells (30, 32, 34, 74–77).

In addition to their deaminase activity, the antiviral activity of A3 proteins can also be conferred through their deaminase-independent activity (Figure 2). Although the catalytic activity of A3G protein is important for HIV-1 inhibition, the N-terminal domain of this protein has the ability to bind to RNAs, although it lacks any catalytic activity (78–81). Owing to this domain, A3G

protein can be packaged in HIV-1 particles, in which it inhibits viral replication through its deaminase-independent activity (78–84). One of the well-known restriction models based on this ability is the "roadblock" model, whereby A3G protein physically blocks the elongation of reverse transcription (82, 83). A3G protein also interacts with HIV-1 reverse transcriptase (RT), thereby preventing reverse transcription (85, 86). Interestingly, the antiviral activity of A3F and A3H proteins has been largely attributed to the deaminase-independent mode (50, 52, 87, 88). An alternative action of A3 proteins is the inhibition of HIV-1 integration. One study highlighted the possibility that A3G protein can interrupt the structural integrity of the HIV-1 pre-integration complex (PIC), as it is reported that A3F and A3G proteins can interact with the integrase protein of HIV-1, thereby inhibiting provirus formation (89). Furthermore, it has been postulated that A3 proteins can interact with host cellular factors through their deaminase-independent activity. Specifically, recent work illustrated that A3B protein can interact with host protein kinase R and RNase L to limit the gene expression of Sendai virus, poliovirus, and Sindbis virus by inactivating host RNA translation *in vitro* (62). Taken together, the antiviral capability of A3 proteins must be measured through their deaminase and deaminase-independent activities.

3 Arms race between A3 proteins and viruses

Heterogeneity in the number of Z domains carried by *A3* genes is predicted to be caused by a gene duplication event (24, 90–93). This event appears to have occurred within a placental mammal ancestor that had already possessed the three types of Z domains (Z1, Z2, and Z3) carried by the present-day human *A3* genes (24, 90–93). Each of the human *A3* genes is composed of a combination of these domains (Figure 1A**).** Intriguingly, the copy number of *A3* genes varies greatly within the mammalian lineage (24, 90–95), suggesting an arms race between placental mammals and genetic threats including endogenous and exogenous retroviruses [reviewed in (5, 19, 69, 96, 97)]. As up to five A3 proteins (A3C-I188, A3D, A3F, A3G, and stable A3H haplotypes) are involved in HIV-1 restriction in human $CD4^+$ T cells and myeloid cells (30, 32, 34, 35, 74–77, 98–100), A3 enzymes have overlapping functions to protect their hosts from various threats. Therefore, it is plausible that the "fortifications" in genes encoding host restriction factors differ because the interaction between the host and pathogen is independent in each mammal. For instance, the mouse genome encodes at least eight TRIM5α-like proteins (101), whereas the human genome encodes only one (102). By contrast, mice have only one A3 protein (92, 103). Thus, it can be said that the seven copies of *A3* genes in humans could be the product of pathogenic pressures imposed on our ancestors.

The same question can also be asked about the pathogens themselves. Because of this "arms race", if viruses had not coevolved with our ancestors, they would have succumbed to the mutagenic properties of A3 proteins. For example, HIV-1 encodes the Vif protein, which can induce degradation of A3 proteins through a proteasome-mediated pathway (34, 35, 65, 71, 75, 98, 104–110), inhibit *A3* mRNA translation (111, 112), and alter the expression of RUNX-regulated genes (113). Vif protein inactivates both deaminase-dependent and deaminase-independent processes. It is hypothesized that HIV-1 Vif evolved to recognize the expansive repertoire of human A3 proteins (114). It is possible that a cross-species jump to primates occurred in an ancestral lentivirus that had originally infected non-primate mammals. As previously explained, mammals have evolved different repertoires of innate restriction factors depending on the individual interactions between themselves and their respective threats. The feline A3 repertoire, containing four genes producing five A3 proteins (114–117), is much simpler than the human A3 repertoire with seven A3 proteins [reviewed in (3, 19, 22, 23)]. The feline lentiviral Vif protein must therefore, have adapted to the A3 repertoire of its new host. This theory is supported by several *in vitro* reports demonstrating that the simian immunodeficiency virus (SIV) Vif protein is still able to degrade feline A3 proteins (117–119). The mechanism through which lentiviral Vif can adapt to an expanded A3 repertoire is termed the "Wobble model" (120) (Figure 3). A zoonotic event causes a partial interaction between the lentiviral Vif and the A3 repertoire of its new host (Figure 3). Initially, a more expansive A3 repertoire may bind to the same recognition site (Figure 3). Over time, "wobbles" may occur, in which Vif adapts and fortifies its interaction with the A3 proteins of its new host (Figure 3). This adaptation event could result in overlapping interaction surfaces of lentiviral Vif with those of A3 proteins, leading to slight differences arising from this independent adaptation event (Figure 3). Over a longer period, the interaction surface shifts drastically because many independent wobble events occur, leading to the current distinct interaction surface between Vif and various human A3 proteins (Figure 3).

The interaction between HIV-1 Vif and the human transcription factor CBF-β (105, 121) is another example of how a virus adapts to a new host. Vif forms an E3 ubiquitin ligase complex consisting of the transcriptional cofactors CBF-β, CUL5, ELOB, ELOC, RBX2, and ARIH2, which allows the viral protein to interact with A3 proteins and induce polyubiquitination, leading to degradation by the 26S proteasome (105, 107, 121–126) (Figure 2). The interaction between Vif and CBF-β was reported to be specific only to HIV-1 and SIVs and not essential for non-primate lentiviruses *in vitro* (127–131). Generally, CBF-β forms heterodimers with RUNX transcription factors to regulate the expression of genes important for hematopoiesis, T-cell development, osteogenesis, and neurogenesis [reviewed in (132–134)]. It has been reported that this recruitment of CBF-β to the E3 ubiquitin ligase complex impacts the heterodimerization of CBF-β with the transcription factor RUNX1 and consequently represses the transcription of genes regulated by RUNX1, one of which is T-bet, a repressor of IL-2 expression (113).

Vif is also reported to be able to interfere with A3G protein translation. A short conserved upstream open reading frame (uORF) located within two secondary structures of *A3G* mRNA is reported to be a negative regulator of A3G protein translation and is crucial for inhibition of translation mediated by Vif (111, 112). HIV-1 Vif requires the presence of this *uORF* in *A3G* mRNA to

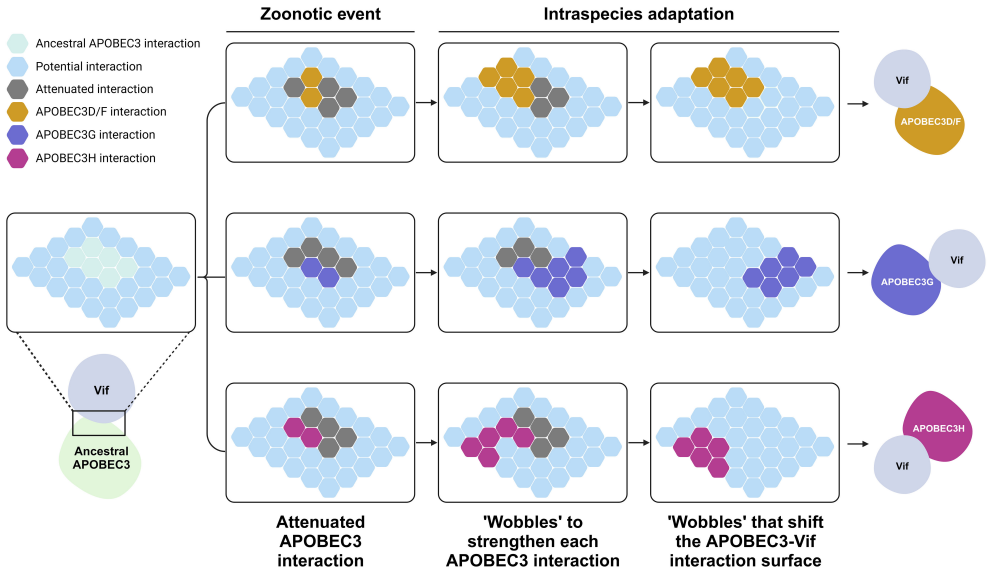

FIGURE 3
Evolution of the interaction between A3 proteins and lentiviral Vif. This schematic is adopted from (120). Each hexagon tiles represent the binding surface of an A3 protein and Vif. Initially, an ancestral A3 protein bound strongly to an ancient lentiviral Vif protein. A cross-species jump to humans occurred, forcing protein to adapt to the wide repertoire of A3 proteins in humans. This resulted in a diminished yet overlapping interaction between Vif and the new repertoire of A3 proteins. Over an evolutionary period, intraspecies adaptation occurred whereby Vif further adapted to its new host, creating wobbles that shifted the binding interface of Vif, resulting in the nonoverlapping interaction surface presently observed between Vif and human A3 proteins. A3, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3; Vif, viral infectivity factor. Created with BioRender.com.

inhibit A3G protein translation (presumably by inhibiting the leaky scanning mechanism of *A3G* mRNAs) and redirect *A3G* mRNAs to stress granules; both these actions reduce global *A3G* mRNA translation (112).

Therefore, it can be said that primate lentiviral Vif has evolved multiple ways to adapt to its new host after presumed cross-species transmission from non-primates. First, primate lentivirus hijacks CBF-β to degrade primate A3 proteins and, coincidentally, perturbs the expression of RUNX-stimulated target genes, presumably also for the benefit of the virus. Second, HIV-1 Vif is able to inhibit the translation of *A3G* mRNAs to prevent (or at least reduce) the packaging of A3 proteins to nascent virions. Collectively, A3 proteins have roles in exerting selection pressure on viruses, thereby facilitating the evolution of the virus in some cases, as will be discussed in the upcoming sections of this review.

4 Implications of A3 proteins as drivers of retrovirus evolution

Retroviruses belong to group VI of the Baltimore classification (135). The genome of retroviruses consists of a homodimer of linear, positive-sense, single-stranded RNA of 7–13 kb in length (136). Unlike most other viruses, retroviruses use an obligate reverse transcription process to convert viral genomic RNA (gRNA) into double-stranded DNA (dsDNA) with long terminal repeats (LTRs). This dsDNA is then integrated into the host genome, resulting in the formation of a provirus, which serves as a template for the transcription of viral RNAs for gRNA and viral protein production (137). During reverse transcription, an ssDNA intermediate is produced. A3 proteins target this ssDNA intermediate as a substrate. In this section, we discuss the implications of A3 proteins as evolutionary drivers of human retroviruses.

4.1 HIV-1

HIV-1 cDNA is the most well-characterized substrate for A3 proteins. A3 proteins induce C-to-U mutations in reverse-transcription ssDNA intermediates, resulting in G-to-A mutations on the genomic strand (Figure 2). These G-to-A mutations can affect more than 10% of all G residues within HIV-1 gRNA, causing an abortive infection attributable to the lethal level of mutations in the HIV-1 genome (73, 138–141). HIV-1 counteracts the antiviral activity of A3 proteins through Vif (Figure 2). Studies examining samples from patients infected with HIV-1 revealed that A3 proteins form a distinct twin gradient of G-to-A hypermutation (142, 143). This gradient is well aligned with the amount of time that the minus-strand DNA remains single-stranded during reverse transcription. The frequency of G-to-A mutations increases away from the primer binding site, reaching a maximum upstream of the 5′-central polypurine tract (cPPT) half-way along the provirus, then reducing significantly, increasing when moving away from the 5′-cPPT and then reaching a maximum upstream of the 3′-PPT of the HIV-1 3′-LTR (142, 143).

An interesting question is whether the mutagenic capability of A3 proteins can aid in virus evolution. Regarding this question, it must first be stressed that G-to-A hypermutation induced by A3 proteins can be beneficial or deleterious for the virus and the host.

The inherent error-prone replication of virus genomic material allows viruses to diversify themselves, permitting the existence of variants that are more fit for replication, including those that can evade the immune system, such as what we currently see in the situation regarding severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (144–151), and those that become resistant to antiviral medications, such as influenza A virus [reviewed in (152)]. This also appears to be the case with A3 proteins. A possible treatment strategy for HIV-1 that focuses on the interplay between A3 and Vif could revolve around the modulation of A3 protein-mediated hypermutation. The theory was predicated on a previous *in vitro* study that demonstrated a proof-of-concept of targeting the A3G–Vif axis to tip the balance in favor of HIV inhibition (153) (Figures 4A, B). In this model, A3-mediated hypermutation (or hypomutation) can be utilized to combat HIV-1 infection (Figure 4). However, a niche between these two extremities that is beneficial for HIV-1 exists because of the existence of a threshold whereby HIV-1 can garner benefits from the mutagenic property of A3 proteins if the action of these proteins is counterbalanced stably by Vif to achieve a certain level of mutagenesis (154–157) (Figures 4A, B). Conversely, the extremities of the A3 mutagenic axes (hypermutation and hypomutation) are deleterious for HIV-1 [reviewed in (28, 158, 159)] (Figures 4A, C, D). For instance, hypomutagenic therapy might work under the assumption that A3 mutagenesis is important and substantial toward the diversification of HIV-1 genome. The idea is that by eliminating this mutagenic potential, HIV-1 cannot sufficiently diversify, allowing the elimination of the virus through the adaptive immune response and antiviral drugs. The premise of the opposite side of this strategy, i.e., hypermutation, is that by modulating A3 activity to induce high levels of mutagenesis, the lethal consequence would eventually eliminate HIV-1 replication, as demonstrated *in vitro* by small-molecule drugs that can upregulate the activity of A3 proteins, resulting in HIV-1 inhibition (153, 160–166). Hypermutated viral cDNA would be subjected to degradation before integration (167). Even if the integration is successful, the cDNA would contain large numbers of missense and nonsense mutations. These proviral DNAs are assumed to be nonreproductive because no progenies or noninfectious viruses will be produced (168–171).

We discussed that A3 can exert mutagenic pressure and that a balance exists between the actions of A3 and Vif (Figure 4). This is because the degradation of A3 proteins by Vif is not absolute, meaning that sublethal mutagenesis can possibly be utilized by HIV-1 to diversify its genome (154, 156, 157, 172, 173). Clinical studies reported that a considerable number of patients infected with HIV-1 at different clinical stages harbored abundant G-to-A hypermutation in proviral DNA (169–171, 174–181), further suggesting that Vif does not eliminate A3 function completely.

Because A3 proteins are mutagens for HIV-1, their potential to confer drug resistance should also be considered. The A3G protein is reported to be a source of genetic variation that confers resistance to 2′,3′-dideoxy-3′-thiacytidine (3TC) *in vitro* and *in vivo* (154, 155). This observation is further supported by an *ex vivo* study using peripheral blood mononuclear cells (PBMCs) obtained from healthy donors (156). Naturally occurring HIV-1 Vif point mutants with suboptimal anti-A3G activity induce the development of proviruses with 3TC resistance and these cytosine deamination mutation events are detected in more than 40% of proviruses with partially defective Vif (156). This partially Vif-defective phenotype can outcompete wild-type virus growth, implying that G-to-A hypermutation alone can alter the phenotype of a viral population. An *in vivo* study using humanized mice found that an isogenic HIV-1 molecular clone with Vif 45G (HIV-45G) had lower replication over time than the wild-type HIV-1 (NL4-3) (155). However, when these mice were treated with 3TC, treatment failure occurred in 91% of mice infected with HIV-45G, which was in clear contrast to the treatment failure of 36% in mice infected with wild-type HIV-1 (155). The mutations attributed to 3TC resistance are M184I (ATG-to-ATA) and M184V (ATG-to-GTG) (155). Although both of these mutations can result from reverse transcription errors, the M184I mutation contains a dinucleotide motif preferred by A3G (ATGG-to-ATAG) (155). Differentiating G-to-A mutations that are derived from either A3 proteins or RT in this mutation is difficult because both can induce G-to-A mutations. However, it is noteworthy that A3G-mediated mutations significantly increase the incidence of 3TC-resistant mutations in humanized mice (155). This agrees with an *in vitro* study demonstrating that the mutation rate of A3 proteins is higher than that of HIV-1 RT (182, 183). Specific patterns can be discerned regarding G-to-A mutations derived from A3 proteins and HIV-1 RT. A study of PBMCs from patients infected with HIV revealed that A3D/F/G/H-derived mutations introduced more stop codons than HIV-1 RT-derived mutations (181). In addition, *in vitro* studies found that HIV-1 RT was biased to the introduction of A-to-G mutations (183, 184), which is fundamentally different to the exclusive G-to-A mutations introduced by A3 proteins. As expected, the result of this difference is that the hypermutation index (A3 protein-mediated G-to-A mutation/100bp) is calculated by subtracting it from the A-to-G mutation rate to correct for background mutation by HIV-1 RT (143).

An *in vitro* study suggested a role for A3 proteins in modulating, but not necessarily conferring, drug resistance (185). It has been argued that A3 proteins have a role in enhancing resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) by inducing a V179I substitution, which arises from a G-to-A mutation (185). In and of itself, V179I does not confer drug resistance. However, when present with the NNRTI resistance mutation Y181C/V, NNRTI resistance is increased by 3-to-8 fold. In addition, the frequency of V179I substitution is higher in $CD4^+$ T cells that express A3F and A3G proteins (185).

A clinical study found that A3G-mediated hypermutation was significantly associated with antiretroviral therapy (ART) failure in Indian patients infected with HIV-1 subtype C (186). However, it should be noted that A3G-mediated hypermutation was only observed in the provirus; no hypermutation was recorded in the plasma HIV RNA of the patients tested (186). This agrees with an *in vitro* study demonstrating that A3G induces purifying selection that will eventually select HIV-1 variants with no hypermutation in their RNA genome that can still produce virions (187). Furthermore, *in vitro* and *in silico* studies support the proposition that A3-mediated hypermutation is an "all or nothing" phenomenon because the

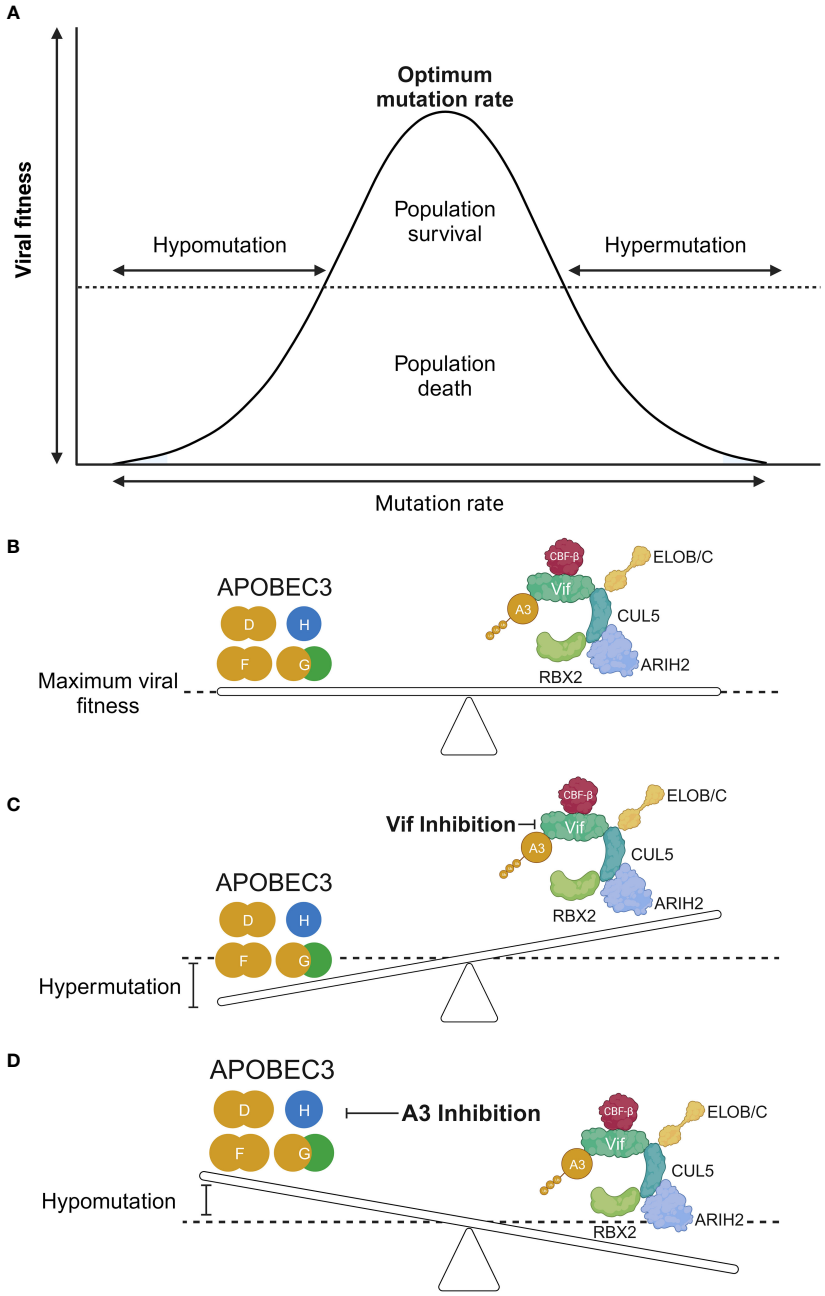

FIGURE 4
The hypomutation and hypermutation activities of A3 proteins. **(A, B)** The interplay between HIV-1 Vif and A3 proteins is an interaction between viral fitness and the mutation rate. An equilibrium between these two axes results in an optimal mutation rate for HIV-1 through the use of A3 proteins as additional sources of mutagenesis. This will achieve a maximum viral fitness greatly exceeding the "dead zone" depicted as a horizontal dotted line along the graph. **(C)** Increased activity of A3 proteins results in hypermutation of the HIV-1 genome, leading to loss of the genome in the population. **(D)** Conversely, it is argued that reduced A3 protein activity results in a less diversified HIV-1 genome, causing it to be more easily eliminated by the adaptive immune response, provided that A3 proteins are important sources of mutagenesis for HIV-1 diversification. RBX2, RING box protein 2; ARIH2, ariadne RBR E3 ubiquitin protein ligase 2; CBF-β, core-binding factor subunit beta; ELOB, elongin B; ELOC, elongin C; Vif, viral infectivity factor; CUL5, cullin-5; A3, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3. Created with BioRender.com.

production of proviruses with A3G-induced sublethal hypermutation (proviruses with low levels of hypermutation yet bearing no stop codons) is statistically very unlikely (188).

Based on the aforementioned clinical study, drug-resistance phenotype derived from A3G-mediated hypermutation was not detected in plasma HIV-1 RNA because it also harbors stop codons due to the deaminating action of A3G in tryptophan codons (TGG-to-TGA/TAA/TAG) (186), further supporting the "all or nothing" phenomenon of A3G-mediated hypermutation. Therefore, it is unlikely that HIV-1 will continue to develop A3-related

mutations under effective ART treatment because a clinical study found no G-to-A hypermutation on plasma HIV-1 RNA in patients with successful ART (186).

Another interesting aspect that A3 proteins can influence is the cytotoxic T lymphocyte (CTL) response against HIV-1 (Figure 5). A3 proteins can introduce changes in the HIV-1 provirus, inadvertently changing the amino acid sequence of a given viral protein (Figure 5A). Therefore, one might also assume that this change will eventually accumulate and generate epitopes that can avoid HIV-1–specific CTL responses. This is supported by a previous *in vitro* report illustrating the inherent trait of A3 proteins as restriction factors that eventually select variants bearing lesser (sublethal) mutations in their genomes because heavily edited genomes would not survive in the population

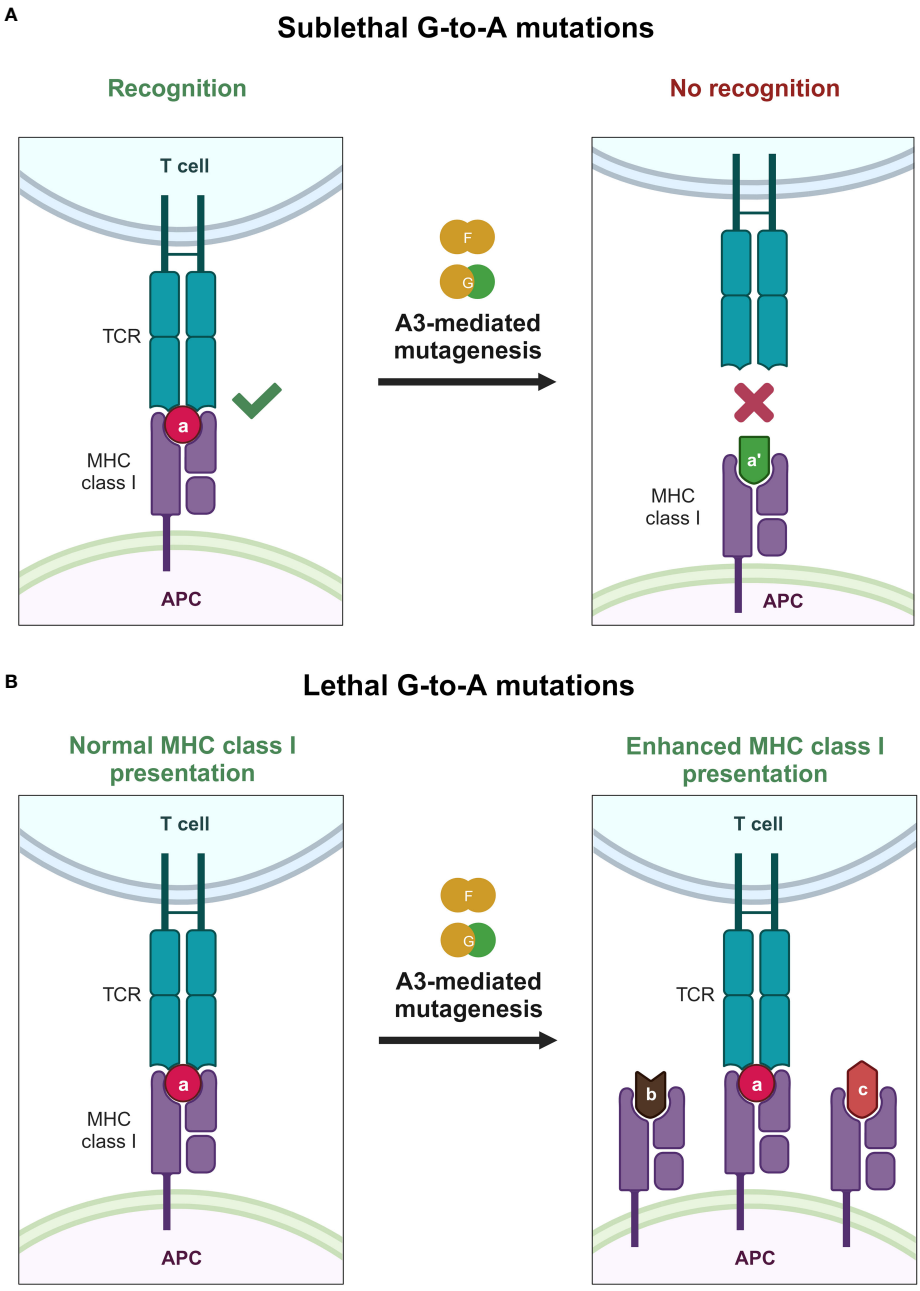

FIGURE 5
Effects of A3 proteins on the CTL response against HIV-1 infection. **(A)** Sublethal mutations mediated by A3F and A3G proteins lead to reduced or even ablated recognition by the CTL because of small changes in the epitope sequence caused by A3F and A3G proteins, depicted by the change of the epitope color and shape. **(B)** Lethal levels of G-to-A mutations mediated by A3F and A3G proteins improve the MHC class I antigen presentation pathway, providing the adaptive immune system with an additional source of antigen, possibly improving detection by the adaptive immune system, as depicted by the increase of MHC class I expression with varying epitope shapes. A3, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3; APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex; TCR, T-cell receptor. Created with BioRender.com.

(187). These variants with minor changes in their genomes could result in overall reduced detection by our adaptive immune response. Along these lines, it was reported that A3F/G-induced mutations on common CTL epitopes cause a reduction in HIV-1–specific CTL responses *ex vivo* (189). Meanwhile, another *ex vivo* study revealed that hypermutation can facilitate detection by CTLs (190) (Figure 5B). Defective proviruses that were heavily edited by A3G protein could produce truncated proteins that can be sources of antigens to CTLs (190). Newly synthesized and rapidly degraded polypeptides [defective ribosomal products (DRiPs)] are major sources of epitopes for major histocompatibility complex (MHC) class I (191). DRiPs are polypeptides with errors in transcription, translation, or post-translational processes [reviewed in (192)]. A previous study demonstrated that targeting HIV-1 group-specific antigen protein (Gag) to the DRiP pathway boosts MHC class I antigen presentation and $CD8^+$ T-cell activation *in vivo* (193). This further demonstrates that A3 proteins have a role in stimulating the adaptive immune response by providing another source of viral antigens for recognition.

Research groups argued that the mutagenicity of A3 proteins is not correlated with the evolutionary pressure from these enzymes (139, 194). If the HIV-1 genome has been changed because of evolutionary pressure from A3 proteins, there should be an imprint left by A3 proteins in the form of an underrepresentation of A3 target motifs and an overrepresentation of A3 product motifs (195). In other words, the nucleotide G must be depleted and A must be enriched in the HIV-1 genome. This is because repetitive exposure to A3 activity can result in nonlethal mutations, leading to the underrepresentation of nucleotide sequences favored by A3 proteins. This underrepresentation is considered a footprint (195). However, this was not found to be the case (194). An explanation based on these two contradicting studies is that G-to-A mutations caused by A3 proteins might not represent the primary mechanism by which they inhibit HIV-1 replication and that they are merely a side product of this inhibition. As previously explained, the antiviral effect of A3 proteins extends beyond their deamination capabilities. Therefore, it is not far-fetched that A3 proteins do not confer any evolutionary pressure on HIV-1. An alternative explanation is that the mutations induced by A3 proteins are highly deleterious, leading to loss of the population. Studies reported that the number of A3G molecules within Vif-deficient HIV-1 virions range from 3–11 (196). This number is greatly reduced to approximately 0.3–0.8 molecules in Vif-proficient virions (197). Furthermore, it was reported that virions packaged with one or two A3G molecules exhibit significantly reduced infectivity (182). This number is close to the number of A3 proteins packaged in virions expressing wild-type Vif. This fuels the hypothesis that the mutagenic property of A3 proteins, as low as it might be, confers a lethal effect on the overall fitness of HIV-1. On average, A3 proteins mutate 2.3 bases for every 1 kb (182). To put things into better perspective, the optimal mutation rate for HIV-1 is agreed to be approximately 0.3 mutations per genome per replication cycle *in vivo* (198). Therefore, it is tempting to think that the mutational burden levied upon the HIV-1 genome by A3 proteins might be too high to tolerate, such that it immediately produces lethal repercussions, leaving no evolutionary footprints on the genome of the surviving HIV-1 in the population. There could be heterogeneity among A3 molecules, including differences in the amount of A3 molecules incorporated per particle and/or the mutation efficiency of A3 proteins in target cells during infection events. Further investigation elucidating whether A3 proteins contribute to HIV-1 evolution is required.

4.2 HTLV-1

Another member of the retrovirus family is human T-lymphotropic virus type 1 (HTLV-1), the causative agent of adult T-cell leukemia (ATL) (199). HTLV-1 was also reported to be susceptible to restriction by A3 proteins (200, 201). Unlike HIV-1, the HTLV-1 genome does not encode Vif. Instead, a peptide motif in the C-terminal of the HTLV-1 nucleocapsid (NC) domain inhibits the packaging of A3G protein into virions, as mutations in this region lead to increased A3G protein packaging and increased susceptibility to this protein (202). Therefore, it is assumed that the mechanism to counteract the antiviral activity of A3 proteins might not be identical to that of HIV-1 Vif. Although endogenous and overexpressed A3G protein could be packaged into nascent HTLV-1 virions in MT-2 and HEK293T cells, few G-to-A hypermutation were observed in the HTLV-1 genome (200). This observation supports the idea that HTLV-1 is relatively more resistant to the antiviral activity of A3 proteins than HIV-1. Another study reported a relatively lower frequency of G-to-A mutations in the HTLV-1 provirus (203). Interestingly, the base composition of HTLV-1 genome is rich in G-C compared with the HIV-1 genome, which is more A-T rich, as reported decades ago (204–208). Therefore, it appears that the frequency of nucleotide preference for the A3 protein within the HTLV-1 provirus is not a major determining factor, given that the HTLV-1 genome has a higher G-C content than HIV-1, but the former is more resistant to A3 proteins. This supports the idea that the difference in replication strategy between HIV-1 and HTLV-1 may be the biggest determinant in A3 susceptibility of HTLV-1. The primary replication route of HTLV-1 *in vivo* is through the mitotic division of host cells because the HTLV-1 provirus is also cloned [reviewed in (209)]. Therefore, ssDNA, as a substrate of A3 proteins, would not be present because of the clonal expansion of HTLV-1-infected cells. Furthermore, it has been reported that the HTLV-1 NC domain in the C-terminus is important for inhibiting the packaging of A3G protein into virions (202). The resistance of HTLV-1 to A3G protein is also evident when considering that, although HTLV-1 RT and HIV-1 RT have comparable mutation rates (210), the diversity of HTLV-1 is lower than that of HIV-1 when comparing the variability of their respective *env* genes (211, 212). These findings provide further emphasis of the greater resistance of HTLV-1 than HIV-1 to the antiviral activity of the A3G protein. Nevertheless, HTLV-1 is still susceptible to A3G protein-mediated deamination during reverse transcription because GG-to-AG

mutations preferred by A3G protein were observed in proviruses from HTLV-1 carriers and patients with ATL (203).

An interesting question is whether HTLV-1 can benefit from A3 mutagenesis because A3 proteins leave a footprint on the genome of HTLV-1 (195, 203). HTLV-1 encodes two oncogenic genes, namely *tax* in the sense (plus) strand and *HTLV-1 bZIP factor* (*HBZ*) in the antisense (minus) strand (213). Tax protein is a potent oncoprotein that is essential for viral transcription and cell transformation (214–216). This protein is highly immunogenic because of the strong inducibility of other viral proteins (217, 218). HBZ is also an oncogenic protein, but it has low immunogenicity (219, 220). Importantly, a previous study by Fan et al. reported that nonsense mutations deriving from the A3G protein occur in minus-strand viral cDNA during reverse transcription, resulting in the inactivation of Tax and all viral proteins excluding HBZ (203). Conversely, G-to-A mutations preferred by A3G protein in the plus-strand region were less frequent, whereas the *HBZ* gene remains intact (203). A nonsense mutation in the *tax* gene of HTLV-1–infected cells would result in the loss of Tax protein expression, which sounds counterproductive to viral infection. However, considering that Tax protein can halt cell cycle progression, losing expression of this protein could confer a growth advantage. An additional explanation is that the loss of Tax protein expression causes the loss of expression of other viral proteins, resulting in escape from the host immune system.

A plethora of studies have been conducted on the interaction between retroviruses and A3 proteins. Results are indicating the role of A3 proteins as drivers of retrovirus evolution, evident in the fact that A3 proteins confer drug resistance and promote immune escape in HIV-1 and promote uncontrolled cell proliferation and immune evasion in HTLV-1–infected cells. Some studies deny the direct contribution of A3 proteins to the aforementioned phenotypes because of their perceived lack of A3-mediated hypermutation in the retrovirus genome. More research should be conducted to ascertain whether the lack of a footprint found in some studies is because A3 proteins do not exert any evolutionary pressure on HIV-1 or because of the lethal mutagenesis induced by A3 proteins in the HIV-1 genome.

5 Implications of A3 proteins as drivers of DNA virus evolution

It is undisputed that A3 proteins can act as antiviral factors against retroviruses. However, A3 proteins are not only antiviral factors for retroviruses. In essence, A3 proteins are DNA mutators, and their best-characterized substrate is HIV-1. DNA viruses belonging to groups I, II, and VII of the Baltimore classification (135) were reported to be susceptible to the mutagenic ability of A3 proteins, as explained later in this review. This lesser-known interaction might not be far-fetched considering that some A3 proteins were reported to be localized to the nucleus (30, 51, 54–62, 66). Therefore, these proteins can physically access viral genomes during DNA virus infection because replication of the genomes of most DNA viruses occurs in the nucleus [reviewed in (221–223)], although some viruses such as poxvirus can replicate in the cytoplasm (224).

5.1 Parvovirus

Parvoviruses have a linear ssDNA genome [reviewed in (225)], which is a prime candidate for a substrate for A3 deamination. It was reported that A3A protein can inhibit parvoviruses (226, 227). However, this inhibition is entirely deamination-independent, as no A3A-induced mutations were observed (226, 227). A3A protein can induce lethal mutagenesis in the genome and prevent survival of the virus in the population, similar to the previously discussed explanation regarding A3 proteins pushing the HIV genome beyond its genomic stability (Figure 4A). However, it is difficult to ascertain whether this is the case, as no studies have confirmed the mutational rate of human parvoviruses. The closest virus belonging to the same family is canine parvovirus, which has a similar mutation rate as RNA viruses (228, 229), implying that A3 proteins can drive the genomes of parvoviruses beyond their genetic stability. The second explanation is that the nucleic acid-binding capability of A3A protein prevented the replication of the parvovirus genome, leading to inhibition (226). This explanation is highly supported by a study demonstrating that the deamination activity of A3A protein is not required for inhibition of parvovirus replication (227).

However, Poulain et al. recorded different results, demonstrating that in the case of parvoviruses, A3 proteins do leave footprints, and there is a difference in terms of the magnitude and localization of the footprint among the viruses within this family *in silico* (195). One of the viruses with the largest A3 protein footprints is the B19 erythroparvovirus (195). This virus was strongly depleted of A3-favored motifs, which has been observed to a lesser extent in parvovirus 4 and bocavirus 4 (195). Interestingly, the researchers found no A3 footprints on adeno-associated dependoparvovirus (195), in accordance with previous *in vitro* reports revealing a lack of A3-induced mutations and the independence of parvovirus replication inhibition from the deaminase activity of A3A protein (226, 227).

If parvoviruses are susceptible to the antiviral activity of A3 proteins, it should be clarified whether they have evolved a mechanism to counteract A3 proteins. However, we found no reports of such an A3 counteraction mechanism by parvoviral proteins akin to Vif protein of HIV-1 or the C-terminal peptide motif of HTLV-1 NC protein. Although it is evident that some viruses belonging to the *Parvoviridae* family are primarily susceptible to the antiviral activity of A3 proteins, whether A3 proteins impart evolutionary pressure on parvoviruses remains unclear. Furthermore, it is unknown whether A3 proteins can help change the phenotype of parvoviruses by conferring drug resistance and/or immune escape.

5.2 Human herpesvirus

Human herpesviruses (HHVs) possess a linear dsDNA genome of 125–240 kbp in length that encodes 70–165 genes (230). DNA replication in HHVs occurs in the nucleus (231). Hence, it is tempting to think that HHVs are susceptible to the antiviral

activity of A3 proteins. A3C protein is reported to be an important restriction factor against human herpesvirus 1 (HSV-1), as indicated by the reduced virus titer and particle/plaque-forming unit ratio upon its overexpression. In addition, A3-edited genomes have been discovered *in vitro* and *in vivo* (232). Furthermore, the same A3-mediated editing was detected in the genome of Epstein–Barr virus (EBV) samples (232). Further fueling this theory, recent reports illustrated that the ribonucleotide reductases (RNRs) of HHVs could antagonize A3 proteins by triggering their relocalization and enzymatic inhibition (51, 59, 233, 234), proving that A3 proteins have a sufficient effect on HHV replication to necessitate a counteraction mechanism.

RNRs synthesize deoxyribonucleoside triphosphates, which are required for DNA replication both by viruses and cells (235). EBV has been reported to antagonize A3B protein through the binding of its RNR subunit BORF2 (51, 59, 233, 234). This binding was reported to enzymatically inhibit the cytosine deaminase activity of A3B protein and relocalize A3B protein from the nucleus to perinuclear bodies to maintain genomic integrity (51, 59, 233, 234). This ability of viral RNR to antagonize the antiviral activity of A3B is argued to be the product of evolution for herpesviruses because it is conserved among viruses that infect humans, who naturally express A3B protein, but it is absent in homologous viruses that infect New World monkeys, which naturally lack the *A3B* gene (233). These results suggest the possibility that A3B protein aided the evolution of HHVs. Furthermore, many of their genes are footprinted by A3 proteins (195).

Another interesting finding is that HHVs that infect lymphocytes, such as varicella zoster virus (VZV), EBV, and Kaposi's sarcoma-associated herpesvirus, do not have reduced A3G protein-preferred motifs *in vitro* (236), even though lymphocytes are known to express extremely high levels of A3G protein (237). This makes sense when considering that HHVs replicate solely in the nucleus (231), whereas A3G protein is primarily localized to the cytoplasm (36, 44, 54, 55, 57, 60) and only a very small amount localize to the nucleus (63–65). VZV, but not HSV-1, is depleted of recognition motifs preferred by A3A, A3B, and A3H proteins (238, 239). Taken together, the depletion of A3-preferred motifs might involve multiple factors that can modulate the frequency of these features. A counterpoint to the notion that A3 proteins aid the evolution of HHVs is a study reporting that although G-to-A hypermutation was found in *in vivo* buccal swabs, they argued that it does not affect HHV genome evolution (232). This connects to the idea mentioned in previous sections of this review in which the highly mutagenic potential of A3 proteins pushed the viral genome beyond its genetic stability, causing the virus to not survive in the population (Figure 4A). Apparently, this might also hold true for HHVs or at least for HSV-1. Although it is true that highly edited genomes are defective, a study monitoring the molecular evolution of herpesviruses found that HSV-1 has 68.3% GC content (240). If A3 proteins contributed to HSV-1 evolution, the percentage should be lower considering the C-to-U mutations that A3 proteins cause on the single-stranded viral DNA.

Therefore, HHVs are demonstrated to be susceptible to the antiviral activity of A3 proteins, and they also possess a counteraction mechanism (51, 59, 233). It can be said that A3 proteins exert evolutionary pressure on HHVs, considering that certain subtypes of HHVs that infect old world monkeys possess a counteraction mechanism against the antiviral activity of A3B protein whereas it is absent in homologous viruses that infect New World monkeys lacking natural A3B protein expression.

5.3 Human papillomavirus

Vartanian et al. sought to clarify whether the human papillomavirus (HPV) genome is susceptible to the antiviral activity of A3 proteins (241). A3H protein is expressed within keratinocytes (target cells of HPV) (241). A3A and A3B proteins are expressed in psoriatic keratinocytes (241), a manifestation that is commonly attributed to HPV infection (242). Prior research focused on the region corresponding to the promoter region of HPV because this region more frequently exists as ssDNA. Hypermutation has been detected in HPV1a plantar wart samples and HPV16 precancerous cervical biopsies, albeit at low cytosine editing frequencies of 11% and 9% for plantar warts and precancerous cervical biopsies, respectively (241). This is supported by a study examining the HPV16, HPV18, and HPV31 genomes (195). However, the researchers found that the footprint left by A3 proteins is genome-wide opposed to being limited to the promoter region (195). This strong presence of an A3 footprint implies that the genome will receive less exposure to A3 proteins, experience less uracil introduction, and consequently less degradation of the viral genome through base excision repair (195). However, an important highlight is the existence of reports of these HPVs stabilizing (243) or even upregulating the expression of A3B protein (244), which is counterproductive for the virus when considering both facts. If the genome of the virus itself is slowly acquiring increased resistance to A3 proteins, why would the proteins encoded in this genome also increase the half-life of A3B protein in an infected cell? Poulain et al. speculated that A3 proteins are required to increase the mutational rate in the HPV genome because the host DNA polymerase hijacked by HPVs is not sufficient to drive viral evolution (195). This might not be far-fetched as a previous publication also suggested a similar narrative (245). Prior research suggested that the TC dinucleotide sequence preferred by several A3 proteins is highly depleted in HPV genomes (195).

HPVs can be roughly categorized into two groups based on tissue tropism. Specifically, beta- and gamma-HPVs infect cutaneous tissues such as the skin, whereas alpha-HPVs infect mucosal tissues such as the cervix (246). Warren et al. found a difference in terms of the basal expression of A3 protein isoforms between cutaneous and mucosal tissues, the latter having extremely high expression of all A3 isoforms excluding A3B (245). They argued that the differential expression of A3 proteins in both types of tissues helps shape the evolution of HPVs, conferring them with

tropism toward one tissue over the other by depleting the TC dinucleotide (245). When considering the various findings, it can be said that A3 proteins exert evolutionary pressure on HPVs.

5.4 Human polyomavirus

Poulain et al. reported that several human PyVs, namely BK polyomavirus (BKPyV), JC polyomavirus, and Merkel cell polyomavirus, are susceptible to the antiviral activity of A3 proteins (195). They found that BKPyV exhibits an extreme depletion of TC dinucleotides, as previously reported (247). Interestingly, BKPyV infection upregulated the expression of A3B protein (247). Similarly as HPV, BKPyV also upregulated the expression of A3B protein, which does not improve nor impair BKPyV infection (247). PyVs upregulate A3B protein via their large T antigen (TaG) (248), although the precise mechanism of the process is unclear. TaG has a domain that targets p53 for inactivation and another domain that targets retinoblastoma protein (RB) for inactivation, leading to the inhibition of cellular apoptosis [reviewed in (249, 250)]. Starrett et al. revealed that the RB-interacting domain is important for *A3B* gene upregulation *in vitro* (248). They proposed a model whereby disruption of the RB–E2F pathway by TaG resulted in the expression of the antiviral enzyme A3B. Reiterating the speculation by Poulain et al. (195), it is highly plausible that DNA viruses such as HPV and PyV utilize A3B protein as a means to evolve their genomes, modulating pathogenesis and/or allowing immune escape. This is further supported by a clinical study demonstrating that A3A and A3B proteins are major sources of mutations in the BKPyV genome (251), implying that A3 proteins act as drivers for BKPyV evolution.

6 Implications of A3 proteins as drivers of hepadnavirus evolution

The most well-studied hepadnavirus affected by A3 proteins is hepatitis B virus (HBV) (195, 252–259). However, there is a debate on exactly when and how A3 proteins exert their antiviral effects. This is because although HBV possesses RT, the process by which it performs reverse transcription is extremely different than that in retroviruses such as HIV-1. The complete synthesis of the plus-strand DNA of the HBV genome does not occur in the producer cell, meaning that a portion of the minus-strand DNA of HBV is exposed as a single strand, making it a prime target for A3 proteins (253). This largely appears to be the case, as a full genome ultra-deep pyrosequencing study revealed that G-to-A hypermutation largely occurs in single-stranded regions of the HBV genome (253). Furthermore, their results point to the contribution of G-to-A hypermutation, which is characteristic of cytosine deamination mediated by A3 proteins, in the progression of HBV infection to liver cirrhosis because there was a correlation between the increased frequency of G-to-A hypermutation and a higher degree of liver fibrosis (253). Another interesting point from that study was the key difference in the action of A3 between hepadnaviruses and retroviruses, as deamination occurs in mature virions within producer cells before viral egress in hepadnaviruses but cells in retroviruses (253).

The aforementioned G-to-A editing that occurs within the HBV genome contributes to HBeAg seroconversion (253). HBeAg seroconversion is a phenomenon whereby the expression of an accessory nonparticulate protein encoded by *preC* mRNA is lost during a natural infection, changing the phenotype from a highly replicative, low-inflammatory phenotype of the HBeAg-positive phase to a low-replicative, HbeAg-negative chronic hepatitis phase (257). This loss of HBeAg protein expression can be considered shortsighted evolution because HBV has to establish an infection (high replication) and then persist (low replication and immune response escape). Interestingly, this G-to-A editing is primarily performed by A3 proteins (253), demonstrating that A3 proteins edit the HBV genome and that these mutations naturally help HBV to establish a persistent infection.

Another aspect is the deaminase-independent activity of A3 proteins against hepadnaviruses. The anti-HBV activity of A3G protein is independent of its DNA editing activity (258), implying that this protein physically blocks DNA strand elongation. This is further supported by the fact that A3G protein interferes with reverse transcription by binding to pre-genome RNA (pgRNA) and preventing nucleocapsid formation (256). However, researchers also found that A3C protein, which is smaller than A3G protein, does not prevent nucleocapsid formation and instead deaminates the HBV genome (256). Another group reported similar findings demonstrating that the blockade of HBV DNA accumulation results from the inhibition of pgRNA packaging (260). Therefore, the next question is whether HBVs have a mechanism to counter A3 proteins. An *in vitro* study demonstrated that the small nonstructural X protein (HBx) of HBV decreases the protein levels of A3G in cells through a process that does not involve proteasomal degradation (255). Interestingly, it was indicated that HBx induces A3G exosome secretion, as the A3G protein concentration was maintained by inhibiting exosome biogenesis (255).

Taken together, the anti-HBV activity of A3 proteins is more of a collective action by several different A3 proteins exerting both deaminase-dependent and deaminase-independent effects to achieve an anti-HBV effect. Considering the evidence that A3 proteins have a role in the evolution of HBV as infection proceeds, it can be said that A3 proteins aid in HBV evolution.

7 Implications of A3 proteins as drivers of RNA virus evolution

The first mention of APOBEC/AID family proteins stems from the discovery of the RNA-editing enzyme A1 (1, 2). A1 protein was later revealed to deaminate DNAs (7). Although A3 proteins generally prefer to deaminate ssDNA, several reports demonstrated that certain A3 proteins induce C-to-U mutation in the ssRNA substrate (261–266). Therefore, it is interesting to speculate that A3 proteins also contribute to RNA virus

evolution. Apparently, this has been observed for a few RNA viruses, as discussed in the subsequent sections.

7.1 Coronaviridae

A study revealed that A3C, A3F, and A3H proteins can inhibit the human coronavirus NL63, a nonzoonotic coronavirus (267). Although hypermutation was not found in the tested coronavirus genome (267), cytosine deamination was still found to occur because the study demonstrated that wild-type A3 proteins confer a higher level of antiviral activity than the catalytically inactive A3 mutants (267). There are two possible explanations for the mechanism by which A3 proteins inhibit coronavirus replication: A3 proteins may deaminate a cellular target or the genome of the coronavirus itself; or, the inhibition may be caused by the interaction of A3 with viral RNA and/or proteins. The antiviral activity of A3 proteins against coronaviruses is supported in another study, which demonstrated marked cytosine deamination in all coronavirus genomes (268), and A3 proteins did have an effect on HKU-1, a nonzoonotic human coronavirus (195). Interestingly, despite being in the same family of coronaviruses, zoonotic coronaviruses such as Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), and SARS-CoV-2, do not contain footprints of A3 proteins (195). For the cases of MERS-CoV and SARS-CoV-1, it was speculated that the relatively low number of infected individuals and the short time of viral circulation may have affected the outcome (195). For SARS-CoV-2, it was stated that the additional viral protein encoded in *ORF10* might have some Vif-like activity through an interaction with the CUL2 ubiquitin ligase to degrade A3 proteins (269). However, this does not eliminate the possibility of deamination, as several study groups have reported the contribution of A3 proteins to UC-to-UU mutations in the SARS-CoV-2 genome (270, 271). The first report of deamination by A3 proteins in the SARS-CoV-2 genome demonstrated that wild-type A3A protein expression greatly increased the viral titer production, by 100-fold (270). Furthermore, SARS-CoV-2 mutants harboring C-to-U mutations were found to be circulating during the early part of the pandemic (January 2020) and rapidly became a signature of the dominant strains (including Delta and Omicron variants) that spread worldwide (270). This is further supported by several reports mentioning that C-to-U mutations are among the most frequently accumulated mutations in the SARS-CoV-2 genome (271–275). A study of the SARS-CoV-2 transcriptome also detected C-to-U mutations and revealed that the sequence context was compatible with APOBEC-mediated deamination (272). In addition, their study indicated that the inherent error-prone RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 represented only a fraction of the C-to-U mutations observed (272).

Collectively, A3 proteins may contribute to the evolution of some coronaviruses, notably SARS-CoV-2. However, a correlation between the A3-mediated deamination of coronaviruses and alteration of their phenotype to confer drug resistance and/or immune escape has not yet been identified, because C-to-U mutations were found in the 5′-UTR, which has an important function in the replication of SARS-CoV-2 RNA and viral protein expression (270). Further investigations examining the role of A3 protein-mediated hypermutation in SARS-CoV-2 evolution, including drug resistance and/or immune escape, are needed.

7.2 Rubella virus

It has been reported that the rubella virus belonging to *Matonaviridae* is susceptible to the RNA-editing activity of A3 proteins (276). The sequence evolution of immunodeficiency-related vaccine-derived rubella virus (iVDRV) revealed a divergence from the genome of the parental rubella virus contained within the vaccine (276). A clear bias toward C-to-U mutations was observed in the iVDRV positive-strand genome, indicating that A3 proteins represent an important cause of the divergence (276). Furthermore, the mutation caused a decrease in nucleotide preference for A3G protein but an increase in nucleotide preference for other A3 proteins and A1 protein, implying that multiple APOBEC family proteins act on iVDRV to generate sequence diversity (276). Similar to a study of coronavirus, the researchers also found that the error-prone RdRp is not the major contributor to this sequence diversity (276). Evidence suggests that rubella virus, at least in immunodeficient patients, is susceptible to the deaminating properties of A3 proteins and that A3 proteins aided the evolution of this virus, as indicated by the changes in its sequence (276). These changes also alter the phenotype of the virus, as different strains of iVDRV have unique replicative and persistence properties (276). Of note, iVDRVs were less cytopathic in cell culture than the parental vaccine virus, but they had better capability to sustain an infection, similar to the characteristics of wild-type rubella virus (276). This strongly supports the idea that A3 proteins can shape the evolution of a virus and even alter its phenotype to improve viral fitness. However, we also note that no other similar studies have confirmed these findings.

The change of iVDRV phenotype allows a higher level of persistence (277). This was later elucidated to primarily stem from A3 protein-derived mutagenesis (276). Therefore, the editing activity of A3 proteins on the rubella virus genome implies that the proteins can shape the evolution of a virus and even alter its phenotype to improve viral fitness.

8 Conclusion

The pathogen–host interaction is a complex “arms race” to outcompete each other for survival. Some viruses have adapted to live with A3 proteins, utilizing their mutagenic ability for their own benefit, whereas some have evolved to negate their action altogether. Therefore, A3 proteins have been established as extremely important restriction factors because of their plethora of interactions with several viruses, helping to shape viral evolution and their own evolution. Modulating A3 proteins for our own benefit remains a difficult task. Because of the deep interactions of A3 proteins with viruses and host proteins, it is difficult to predict

the repercussions of modulating these proteins, as it can lead to unwanted outcomes or even promote beneficial mutation in viruses. More research is needed to better elucidate the interactions of A3 proteins with host and pathogens.

Author contributions

MJ: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. TI: Conceptualization, Funding acquisition, Investigation, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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