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APOBEC3 Proteins in Viral Immunity

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Abstract

Apolipoprotein B Editing Complex (APOBEC3) family members are cytidine deaminases that play important roles in intrinsic responses to infection by retroviruses and have also been implicated in the control of other viruses such as parvoviruses, herpesviruses, papillomaviruses, hepatitis B virus and retrotransposons. While their direct effect on modification of viral DNA has been clearly demonstrated, whether they play additional roles in innate and adaptive immunity to viruses is less clear. Here we review the data regarding the various steps in the innate and adaptive immune response to virus infection in which APOBEC3 proteins have been implicated.

The genomes of mammals and other species contain many genes that restrict infection by viruses. Many antiviral intrinsic restriction factors were discovered through the identification of viral gene products that counteract their action. For example, Apolipoprotein B editing complex 3G (APOBEC3G), a cytidine deaminase (CDA) belonging to the activation-induced CDA (*AIDCDA*)/*APOBEC* gene family, was found because the human immunodeficiency virus (HIV)-1-encoded viral infectivity factor (Vif) blocks its activity (1, 6). Many host antiviral genes, including those in the *APOBEC3* family, have undergone positive selection by infectious pathogens, resulting in polymorphisms in both regulatory and coding regions (2-5). In addition to the sequence heterogeneity found in polymorphic alleles within a given species, the number of *APOBEC3* genes in different species varies due to expansion or contraction of the locus, ranging from 1 gene in mice and rats to 7 in primates (*APOBEC3A*, *APOBEC3B*, *APOBEC3C*, *APOBECDE*, *APOBEC3F*, *APOBEC3G* and *APOBEC3H*) (3, 5-10). Polymorphisms in the mouse *Apobec3* gene have been linked to susceptibility to infection by murine retroviruses (11-13), while at least one polymorphic *APOBEC3H* allele (HapII) is believed to confer resistance to HIV-1 infection and disease progression; genome-wide association studies have also implicated other human *APOBEC3* polymorphisms in HIV-induced disease (11, 14-19). Since HIV is a relatively recent virus in humans, it is likely that other infectious agents contributed to the positive selection of *APOBEC3*s.

APOBEC3 proteins inhibit replication of HIV-1 lacking *vif*, which encodes a 23kD protein (1, 20-23). 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-β, Cul5 and elongins. This

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prevents APOBEC3 packaging and thereby overcomes the antiviral activity (24-30). In contrast, in producer cells infected with *vif*-deficient-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 (31-35).

Once packaged, APOBEC3 proteins inhibit infection by deaminating deoxycytidine residues on minus strand DNA produced by reverse transcription, introducing G-to-A mutations in newly synthesized HIV-1 coding strand DNA. This leads to both degradation of reversed transcribed DNA prior to integration and to lethal G to A coding strand mutations in the integrated provirus (36). APOBEC3G most often deaminates C residues in CC motifs, while the other APOBEC3 proteins preferentially modify those found in CT motifs (20, 37, 38). Because APOBEC3G-induced mutations commonly occur in TGG motifs, deamination often converts the tryptophan codon TGG to a TAG stop codon; in contrast, the other human APOBEC3 proteins, as well as mouse APOBEC3, generate GAA or GA to AAA and AA mutations, which more frequently result in missense mutations (22, 39, 40). APOBEC3-mediated sub-lethal mutagenesis could lead to both drug-resistant and immune escape viruses and lethal mutations may result in the production of truncated viral proteins degraded by the cell's proteolytic processing pathways, thereby increasing antigen presentation (see APOBEC3 proteins and Adaptive Immune Responses, below) (41).

APOBEC3 proteins also inhibit virus replication by CDA-independent mechanisms (42) (Fig. 1). For example, APOBEC3F lacking CDA activity is as effective as the wild type protein in inhibiting HIV-1 infection, at least in cultured cells (43). *In vitro* studies have suggested that APOBEC3 proteins inhibit elongation and accumulation of HIV-1, murine leukemia virus (MLV) and mouse mammary tumor virus (MMTV) reverse transcription products (44-46). APOBEC3 proteins also inhibit infection by parvoviruses, as well as retroelement mobilization, without extensively hypermutating their genomes (47-51).

While virion-packaged proteins appear to restrict infection of T cells, APOBEC3 proteins expressed in human and mouse myeloid and dendritic cells also can restrict incoming HIV, MMTV and MLV by both CDA-dependent and -independent means (52-57). APOBEC3 proteins have also been implicated in hyper-mutating and restricting the hepadnavirus hepatitis B virus (HBV) and human papillomavirus (HPV) in hepatocytes and keratinocytes, respectively, as well as the herpes simplex virus-1 (HSV-1) and Epstein Barr virus (EBV) in established cell lines and primary patient samples (58-60); whether this is the result of target cell APOBEC3 activity or packaged viruses in the case of these other virus families is not known.

APOBEC3 expression in cells of the immune system

The different APOBEC3 proteins are expressed to varying levels in hematopoietic cell populations, including $CD4^+$ and $CD8^+$ T cell subsets (e.g. naïve and memory), B cells, and myeloid cells (55, 61, 62). $CD4^+$ 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 (63). Moreover, HIV-1 proviral DNA hypermutation combined with increased

APOBEC3G expression levels has been linked to lower virus replication and increased $CD4^+$ T cells counts in patients (64-67), although individuals carrying the anti-HIV-1 *APOBEC3H* HapII allele also display lower levels of infection and higher $CD4^+$ T cells counts compared to individuals carrying other *APOBEC3H* alleles (14). More recent work suggests that both cytidine deamination and reverse transcription inhibition play a role HIV-1 restriction in primary $CD4^+$ T cells (63).

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 antigen-presenting cells (APCs) (68). However, macrophages are relatively resistant to retrovirus infection due to the expression of not only APOBEC3 proteins but additional cell host restriction factors, such as SAM domain and HD domain-containing protein 1 (SAMHD1); the latter is believed to deplete the dNTP pools available to reverse transcriptase for viral cDNA synthesis (69-72). Macrophages express APOBEC3G, APOBEC3F and APOBEC3DE and their upregulation is IFNα-dependent, although APOBEC3G restricts HIV-1 more potently than the combined effect of APOBEC3F and APOBEC3DE in this cell type (62, 73). Target-cell expression in primary macrophages may also play a role in restricting HIV as well as other retroviruses (45, 54, 55). APOBEC3A is also expressed at the high levels in monocytes, while fully differentiated macrophages express low levels (74); however, macrophage expression of APOBEC3A is strongly enhanced by IFNα treatment (55, 62, 74). 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 (69, 74). APOBEC3G induction by IFNα in CD14+ monocytes is also significantly higher in HIV-1-exposed but seronegative individuals than in HIV-infected individuals or healthy controls (75). Only a small percentage (≤ 6%) of HIV-1 sequences from infected macrophages contain G to A hypermutations; thus, it is possible that APOBEC3 restriction of lentiviruses in macrophages occurs primarily by CDA-independent means (55).

Immature myeloid dendritic cells (DCs) can be productively infected by HIV-1; these cells may also be used by HIV-1 as a “Trojan Horse” to allow for the transmission of virus to the lymph nodes, thus bringing it in the proximity of T cells (76, 77). Transmission of virus from DCs to T cells likely occurs by direct cell-cell transmission via immunological synapses (78, 79). Myeloid DCs however support only a limited amount of HIV replication; at least in part, this has been attributed to cell host restriction factors such as APOBEC3 proteins. Activation of myeloid DCs by IFNα results in the potent upregulation of APOBEC3A, APOBEC3F, and APOBEC3G, without the induction of signals that lead to their maturation (80-82). Unlike macrophages, HIV-1 DNA in myeloid DCs is hypermutated upon IFNα treatment; transmission from myeloid DCs to T cells is significantly reduced compared to IFN-naïve cells (80).

B cell expression of APOBEC3G is higher than that seen in monocytes (62); nevertheless, because B cells lack the entry receptors required for HIV-1 infection, APOBEC3G is unlikely to play a role in cell-intrinsic restriction. B cells, however, are a major source of exosome production upon CD40L and IL4 stimulation (83). APOBEC3G has been shown to be a major exosomal component and exosomes bearing APOBEC3G can confer anti-HIV-1

activity to Jurkat T cells (84). APOBEC3G levels are upregulated upon treatment of B cells with a combination of agonists such as CD40L, IL-4 and anti-HLA- class II antibodies and autologous $CD4^+$ T cells co-cultured with B cells activated with these agonists are significantly less infected by HIV-1 (85). This suggests that APOBEC3G derived from exosomes produced by activated B cells confers antiviral activity to $CD4^+$ T cells (85). B cell-expressed APOBEC3 proteins may also act on other viruses, which infect this cell type, such as EBV (58).

APOBEC3 and the innate immune response

As discussed, APOBEC3 genes are interferon-stimulated genes (ISGs) whose expression is increased in response to various stimuli, including the ligands of Toll-like receptors TLR3, TLR4 and TLR7 (52, 80, 81, 86-90). Thus, the activation of innate immune responses that occurs upon infection with many different viruses could lead to increased APOBEC3 activity. This might especially be important for combating viruses acquired at mucosal sites of infection, where sentinel cell targets such as macrophages and dendritic cells are poised to mount such responses.

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 (reviewed in (91)). Studies have shown 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 (ALR) family that subsequently signal through the stimulator of interferon genes (STING) pathway (92-94). As described above, APOBEC3 proteins inhibit reverse transcription in addition to introducing CDA-induced mutations. APOBEC3-mediated inhibition of reverse transcriptions would thus seemingly limit cytosolic sensing and the IFN-induced antiviral response. Indeed, we recently showed that in mice, APOBEC3 in macrophages limits levels of retroviral reverse transcripts that trigger cytosolic sensing (94). However, reverse transcripts that escaped this blockade activate the STING pathway via cytosolic sensing and induce 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 herpesviruses 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. This interplay between innate immune sensors and APOBEC3 is likely to afford multiple layers of protection to host against infection by multiple different virus families.

APOBEC3G has also been linked to increased destruction of HIV-1 infected cells by natural killer (NK) cells (95). 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. This in turn generates gaps or breaks in DNA and subsequently induces the DNA-damage response, a known inducer of NKG2D ligand expression (95). Thus, another antiviral function of APOBEC3G may be to recruit lymphocyte effectors such as NK cells, which in turn eliminate infected cells. Whether other human APOBEC3 proteins also affect NK recognition of HIV or other virus-infected cells remains to be determined.

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, namely by affecting the generation of cytotoxic T lymphocytes (CTLs) that recognize viral peptides and perhaps B cell production of antiviral antibodies. Because APOBEC3 expression is induced by virus infection of APCs, as discussed above, this may afford additional layers of host protection.

It is well-known that viruses causing persistent infection, like HIV-1, generate escape variants. HIV may take advantage of non-lethal mutations induced by APOBEC3 proteins to generate such CTL escape variants (96); 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 (39, 40). Thus, it may be beneficial for the virus to preserve APOBEC3G mutation hotspots at locations that influence the presentation and recognition of T cell epitopes and thereby aid in immune escape. 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 (97, 98).

CTL responses to viruses may also be increased through APOBEC3G-generated stop codons leading to premature truncation of proteins and degradation via antigen-processing pathways in HIV-1 infected cells (99, 100). Indeed, the virus-specific CTL response to APOBEC3G-expressing, HIV-infected APCs is increased compared with APCs that don't express the CDA (100). 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 (39). In this case, missense mutations in viral proteins could also lead to misfolding and protein degradation. Indeed, for many viruses including HIV-1, there is an inverse correlation between CTL response and viremia and disease progression (101, 102). 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 antibodies may also be altered by APOBEC3 proteins. APOBEC3 knockout mice generate neutralizing antibodies against Friend murine leukemia virus (FV) with significantly slower kinetics than wild-type mice, although the responses in APOBEC3 knockout mice eventually become as high as those in wild type animals (13, 103) . 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 antigen load and the induction of immune tolerance or prevent FV-mediated damage of critical hematopoietic lineage cells required for generating an immune response (103, 104).

APOBEC3 may play also a role in somatic hypermutation of antibodies. AID is the primary CDA involved in somatic hypermutation of immunoglobulin genes that results in the diverse repertoire of antibodies needed to clear infections (105). One study found that the Ig heavy-chain (IgH) sequences of FV-specific monoclonal antibodies derived from APOBEC3 knockout mice had significantly lower levels of C-to-T and G-to-A somatic hypermutation and lower virus-binding ability than those from wild type mice (106). However, it is not clear that Ig somatic mutations are critical for the control of FV, since AID knockout mice produce virus-neutralizing IgM antibodies and control infection (107). Nevertheless, since the human APOBEC3 protein APOBEC3A and APOBEC3B have been implicated in mutating genomic DNA, it is possible that they contribute to the development of neutralizing antibodies during virus infection (108, 109).

Conclusions

Organisms adapt to infectious agents by developing protective responses and conversely, infectious agents develop adaptive countermeasures to these responses. Host defenses against infectious agents include various mechanisms of innate immunity (e.g. NK cells, the Toll-like receptors and interferons) and adaptive immunity (humoral and cell-mediated). APOBEC3 proteins have clear roles in conferring intrinsic host resistance to infection to different viruses due to their ability to directly act on viral genomes, thereby generating mutations or blocking viral nucleic acid synthesis. There is also a body of evidence, particularly in the case of retroviruses, that APOBEC3 deaminase activity plays additional anti-viral roles in innate and adaptive immunity. Whether these additional mechanisms operate in the anti-viral response to other virus families remains to be determined. Moreover, it will be important to demonstrate that these additional roles for APOBEC3 proteins function in the context of virus infection *in vivo*.

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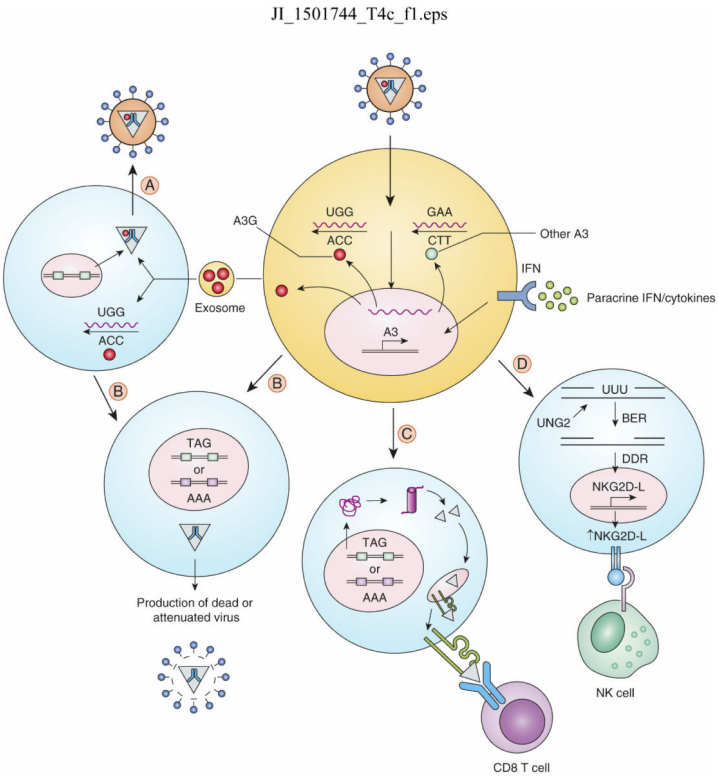

Figure 1.

Role of APOBEC3 proteins in anti-viral immunity. APOBEC3 proteins are ISGs, whose expression is induced by IFNs and other chemokines/cytokines produced by cells in response to infection. APOBEC3 molecules are either packaged into virions or produced by the target cell, leading to deamination of cytosine residues in viral reverse-transcribed DNA; this leads to the generation of stop codons, in the case of A3G (red molecule) or missense mutations with the other A3 proteins (blue molecule). Certain cells, such as B cells, may also shed APOBEC3 in exosomes, which can be transmitted to virus-infected cells and either be packaged into viruses (A) or deaminate viral reverse transcripts which then integrate into the genome. These cells, as well as cells directly infected with virions containing packaged A3 (B), produce dead or attenuated viruses. When APCs are infected (C), the introduction of mutations generates truncated or misfolded proteins, which are degraded by the proteasome and provide MHC-I epitopes leading to increased CTL responses and destruction of infected cells. In other cells (D), U residues in DNA generated by APOBEC3-mediated deamination are cleaved by UNG2, generating gaps that are acted upon by the cell's base excision repair (BER) machinery, triggering a DNA damage response (DDR). This in turn induces increases NK ligand expression and NK-mediated killing of infected cells.