Review article
Tactics used by HIV-1 to evade host innate, adaptive, and intrinsic immunities

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Keywords: human immunodeficiency virus; immune evasion; natural killer; antibody; cytotoxic T lymphocytes

Objective To review the mechanisms by which HIV evades different components of the host immune system.

Data sources This review is based on data obtained from published articles from 1991 to 2012. To perform the PubMed literature search, the following key words were input: HIV and immune evasion.

Study selection Articles containing information related to HIV immune evasion were selected.

Results Although HIV is able to induce vigorous antiviral immune responses, viral replication cannot be fully controlled, and neither pre-existing infected cells nor latent HIV infection can be completely eradicated. Like many other enveloped viruses, HIV can escape recognition by the innate and adaptive immune systems. Recent findings have demonstrated that HIV can also successfully evade host restriction factors, the components of intrinsic immune system, such as APOBEC3G (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G), TRIM5α (tripartite motif 5-α), tetherin, and SAMHD1 (SAM-domain HD-domain containing protein).

Conclusions HIV immune evasion plays an important role in HIV pathogenesis. Fully understanding the tactics deployed by HIV to evade various components of the host immune systems will allow for the development of novel strategies aimed toward the prevention and cure of HIV/AIDS.

After 30 years of research, a vast amount of information has been amassed to explain the pathogenesis, structure, and immunobiology of the human immunodeficiency virus (HIV). Based on this body of knowledge, great strides have been made in the development of drug therapies that have dramatically decreased mortality and prevented transmission. However, HIV remains an intransigent pandemic threat. More than 60 million people have been infected by HIV with 25 million deaths since the disease was first identified in the early 1980s, serving as a stark reminder that continued efforts are required in the search for a cure or a vaccine. To date, however, several efforts to develop an effective vaccine have failed or shown only low efficacy. Therefore, it is worthwhile investigating the mechanisms by which HIV escapes or evades components of the innate/adaptive/intrinsic immune systems.

Eukaryotic organisms have been exposed to viral infections for millions of years. This coevolutionary process has driven the development of innate and acquired, or adaptive, immune systems against invading viruses. In turn, viruses have evolved countermeasures to escape immune control. A set of different accessory proteins is encoded by HIV genomes to perform this job so that HIV can readily replicate in the specific cell environment.

For example, the accessory protein Vpx is found exclusively in HIV-2 and some simian immunodeficiency viruses (SIV). Interestingly, Vpx can even enhance HIV-1 infection in dendritic cells (DCs) and macrophages, and it is, moreover, able to promote the accumulation of full-length viral DNA.

In addition to the innate and adaptive immune systems, humans and other mammal hosts have also developed the intrinsic immunity or host restriction factors during the long history of combating pathogenic microbes. Intrinsic immunity refers to a series of cellular-based antiviral defense machineries, including those genetically encoded proteins specifically targeting eukaryotic retroviruses. The intrinsic immune proteins, such as host restriction factors, can be expressed at a constant level to halt viral infection promptly. Thus far, four major classes of retroviral restriction factors have been identified, including the apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G (APOBEC3G), the first host gene identified as an inhibitor of HIV-1 infection, tripartite motif 5-α (TRIM5α), tetherin, also known as BST-2,
At the same time, HIV has also developed tactics to antagonize these antiviral host restriction factors through its accessory proteins, including, for example, the HIV Vif and Vpu proteins as the antagonists of APOBEC3G and tetherin, respectively.\(^16\)

In this review, we summarize and discuss the advancements made in the study of the host immune system and the mechanisms used by HIV to evade it.

**HIV ESCAPES FROM THE INNATE IMMUNE SYSTEM**

Innate immunity is a first-line defense against HIV infection and contributes to the control of early viral pathogenesis. Natural killer (NK) cells and complement immunity are vital components of the innate immune system, and they provide very different methods to defend against HIV infection. NK cells respond to HIV infection by cytolytic and noncytolytic mechanisms. Although HIV-infected target cells lack expression of major histocompatibility complex (MHC) molecules, activated NK cells can lyse them by perforin and granzymes. It is notable that NK cells also secrete several chemokines, such as CC-chemokine ligand3 (CCL3), CCL4 and CCL5, or cytokines, such as interferon-\(\gamma\), to antagonize HIV infection via noncytolytic control. As a part of innate immunity, the complement system promotes the ability of antibodies and phagocytes to clear pathogens from an organism. However, its activation is multifaceted, involving a number of blood-borne small proteins.

**NATURAL KILLER (NK) CELLS**

NK cells play an important role in controlling HIV-1 infections through different mechanisms. It has been reported that a slow progression of AIDS is associated with the combined expression of the killer immunoglobulin-like receptor (KIR) 3DS1, which is an activating natural killer (NK) cell receptor, and human leukocyte antigen (HLA)-B Bw4-80I, as its presumed ligand. Notably, the KIR3DS1-expressing NK cells exhibited strong inhibition of HIV-1 replication in target cells that express HLA-B Bw4-80I, indicating that variation at the KIR focus affects the effectiveness of NK cell activity against HIV-1 infection.\(^20\) Most recently, Alter et al.\(^20\) reported the presence of KIR-associated amino acid polymorphisms in HIV-1 sequences isolated from chronically infected individuals and demonstrated their ability to enhance the binding of inhibitory KIRs to HIV-1-infected CD4\(^+\) T cells, resulting in a reduction of antiviral activity in KIR-positive NK cells. These findings suggest that HIV-1 can evade NK cell recognition by selecting sequence polymorphisms within regions targeted by KIRs.

Viruses use multiple strategies to evade the response of NK cells, and HIV is no exception. To implement its evasive strategy, HIV uses negative factor (Nef) protein to down-regulate the expression of MHC and non-MHC ligands for NKR, resulting in the reduction of the NK cell-mediated anti-HIV activity.\(^21\) Furthermore, HIV can modulate NK cell differentiation and maturation, promote apoptosis of NK cells, as well as dysregulate the expression of NKR and the production of NK cell-activating cytokines.

**COMPLEMENTS**

As suggested above, activation of the complement system, which is a component of innate/adaptive immunity, with a powerful capacity to lyse pathogens, including HIV, can basically be divided into four pathways: the classical pathway, the mannos-binding lectin (MBL) pathway, the alternative pathway and the membrane lytic pathway. The binding of antibody to antibody can trigger the complement system via the classical pathway, while cleavage of C3 and C5 proteins is an alternative pathway for activation. The end result of activation by both the classical and alternative pathways is the formation of the membrane-attack complex (MAC), which forms transmembrane channels, resulting in the lysis of virions or virus-infected cells. Extensive evidence demonstrates that the complement system deploys antibody-mediated, complement-dependent lysis against challenge by HIV. However, such deployment in the defense against HIV infection is a sword with two edges. On the one hand, complement can promote the removal of HIV virus and neutralization of HIV-1 particles. On the other hand, it can enhance HIV infectivity by mediating the attachment of virus to specific cells, such as macrophages or dendritic cells, which express complement receptor CR3 and CR4, in turn resulting in expanding the source of HIV-infected cells and facilitating the spread of the virus. Thus, as a strategy to evade complement-mediated destruction, HIV can, in fact, enhance its coverage by complement receptor, further incorporating complement receptors CD55, CD59 and CD46 into its membrane to resist complement-mediated lysis.\(^22\)

**HIV ESCAPES FROM THE ADAPTIVE IMMUNE SYSTEMS**

**Neutralizing antibodies**

HIV infection elicits multiple antibodies. Some of them are broadly neutralizing antibodies which have the potential to protect against AIDS virus infection. Although the underlying mechanism remains unclear, the humoral immune response is still responsible for controlling HIV infection. Accordingly, binding with neutralizing antibodies may interrupt the interaction between HIV and receptors on the susceptible cell surface, permitting the engagement of Fc receptor-mediated phagocytosis. Thus far, a number of broadly neutralizing monoclonal antibodies (mAbs) have
been identified. For instance, b12 and VRC01 bind to the CD4-binding site on gp120, and 2G12 binds to the glycan configuration on the outer domain of gp120. 2F5, Z13e1, 4E10, and 10E8 bind at the membrane-proximal external region (MPER) on gp41, which is a very conserved site in gp41, while PG9 and PGT128 bind to the V3 regions of gp120.

Two strategies are commonly used by HIV to evade neutralizing antibodies. One is rapid mutation. Because it takes time to produce antibodies against HIV, rapid mutation makes it impossible for the immune system to immediately produce a corresponding antibody, thus enabling HIV to successfully evade antibody response. Second, the viral envelope (Env) is heavily glycosylated. In fact, almost 50% of the mass of gp120, the surface moiety of the HIV-1 Env, is carbohydrate. This modification results in masking critical epitopes. Moreover, numbers of neutralizing antibodies target the regions of the Env that are only transiently exposed at the time of viral entry, just when the glycoprotein is ready to mediate the fusion between viral and cellular membranes. Thus, once again, HIV has configured a tactic that successfully evades risk to its replication.

**Cytotoxic T lymphocytes (CTLs)**

CTLs play a critical role in the host’s anti-HIV immune response. CTLs interact with the MHC-I molecules present on the surface of infected cells. CTLs depend on the granule-independent pathway involving Fas/FasL interaction and the perforin pathway to kill the infected cells. Again, however, viral mutation is the major HIV evasive stratagem. By its tolerance for sequence variability and lack of fidelity of viral reverse transcriptase, the HIV antigenic repertoire can form polymorphisms, particularly in the viral Env. On average, each time the 10 kb HIV genome is replicated and one nucleotide substitution results in masking critical epitopes.

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**HIV EVADES AGAINST INTRINSIC IMMUNE SYSTEM**

Starting from the early 2000s, more and more evidence has demonstrated that HIV-1 infection can be affected by host restriction factors and that some viral accessory proteins function as their antagonists. For example, APOBEC3G was identified as the first host restriction factor that potently inhibits HIV-1 infection, but its antiviral activity was found to be suppressed by the Vif protein. Subsequently, a variety of anti-HIV restriction factors and their antagonists have been discovered.

**APOBEC3G**

APOBEC3G (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G) is the first host restriction factor against HIV discovered by Sheehy et al in 2002. They found that APOBEC3G could inhibit HIV DNA synthesis in the absence of Vif. As a cytidine deaminase, APOBEC3G suppresses HIV transcription by substituting G to A in the HIV genome. Upon contact with the GG dinucleotides, APOBEC3G changes TGG (coding for Trp) to TAA (stop codon), stopping the translation of the viral protein. However, HIV can recruit Vif to induce the ubiquitin-dependent degradation of APOBEC3G by linking a cullin 5-based E3 ubiquitin ligase complex to APOBEC3G proteins, resulting in the degradation of APOBEC3G in proteasomes and preventing the encapsidation of APOBEC3G into viral particles. In addition, the virus makes use of the special characteristic of APOBEC3G to promote mutations when APOBEC3G-mediated mutations are at a low level.

**TRIM5α**

TRIM5α (tripartite motif 5-α) is an important determinant of resistance first found in monkey cells. TRIM5α controls viral replication by binding to viral capsids in the cytoplasm and interrupting their coating procedure, which is important because capsid uncoating time is critical for retroviruses. Hence, if the process is delayed or blocked, the preintegrated complex will not enter the nucleus of target cells, and if the process is accelerated, the virus capsid...
protein will be degraded, and the reverse transcription process will be terminated. However, HIV can escape from attack by TRIM5α by mutating the sequence of the viral capsid protein so that the viral capsid cannot be bound by TRIM5α.47

**Tetherin**

Tetherin, also named BST-2 (bone marrow stromal antigen 2), CD317, or HM1.24, is the newest host restriction factor identified by Neil and Bieniasz.48 In the absence of HIV-1 viral protein U (Vpu), tetherin is a host cellular protein which inhibits HIV infection by preventing the virus from releasing mature virions to the cell surface.50 While tetherin is not expressed in primary CD4+ T cells, it can be highly induced by type I interferons.50 However, Vpu plays an important role as an antagonist to tetherin. Vpu is a 16 kDa protein which is produced together with Env. Vpu functions to recruit ubiquitin ligase complex to mediate polyubiquitinylation and proteasomal degradation and help release mature viral particles.51 While we also now know that Vpu helps to keep tetherin away from the virion budding sites, the exact mechanism of antagonism still needs further study. In addition, recent study showed that HIV replication is hypersensitive to IFN-α if Vpu is absent, and effective replication is dependent on Vpu for both in vivo- and ex vivo-infected human lymphoid tissues.52

**SAMHD1**

HIV-1 and the related primate lentiviruses HIV-2 and SIV infect cells that express CD4 and an appropriate chemokine receptor, CCR5 or CXCR4. However, the magnitude of infection with HIV-1 is cell type-specific. The activated human CD4+ T cells are much more susceptible to infection with HIV-1 than human myeloid-lineage cells, such as macrophages and dendritic cells (DCs).53 However, DCs have a unique capacity to take up intact viral particles and hand them off to susceptible T cells, thus enhancing T cell infection in trans. This phenomenon of trans enhancement highlights the ability of HIV-1 to potentially exploit the cellular trafficking machinery of DCs, while, at the same time, avoiding activation of the innate immune recognition pathways in these cells.54 Recent studies have demonstrated that a myeloid cell-specific dominant restriction factor, the SAM-domain HD-domain containing protein 1 (SAMHD1), is able to limit the extent of reverse transcription following viral entry. The restriction also limited infection with HIV-2 and SIVmac as long as these viruses were defective for the accessory protein viral protein X (Vpx), which is not encoded by HIV-1. The Vpx proteins from HIV-2 and SIV render human myeloid-lineage cells permissive to HIV-1 infection through proteasomal degradation of SAMHD1.55,56 Delivery of Vpx by virus-like particles (VLPs) resulted in the reversal of HIV-1 infection of DCs. In addition, Vpx could also reverse the inhibition of HIV-1 infection in macrophages, as mediated by SAMHD1. The inhibition of HIV-1 infection in macrophages could be overcome by coinfection with Vpx containing SIVsm VLP.57 Hrecka et al58 used a Flag HA-tagged Vpx protein as bait to pull down potential binding proteins for Vpx. Using a combination of tandem affinity purification and electrophoresis followed by mass spectrometry, they have found that SAMHD1 is the major interacting protein. They then showed that SAMHD1 is highly expressed in HIV-1 nonpermissive cells, whereas it is absent in a range of HIV-1-sensitive cell lines, such as Jurkat and SupT1. They further proved the mechanism by which Vpx induces SAMHD1 degradation, namely that Vpx causes relocalization of SAMHD1 to the cytoplasm prior to routing toward the proteasomal machinery. Using overexpression and RNAi approaches, Laguette et al59 showed that SAMHD1 is required in differentiated THP-1 cells, macrophages, and monocyte-derived dendritic cells for restriction of HIV-1 infection. The restriction does not occur in SAMHD1-expressing THP-1 cells when they are cycling; instead, it requires differentiation-induced cell-cycle arrest. This observation suggests that the restriction may apply to a broader category of noncycling cells, such as resting CD4+ T lymphocytes.

Like human myeloid-lineage cells, resting CD4+ T cells are also refractory to HIV-1 infection, while activated CD4+ T cells are permissive to HIV-1 infection. Most recently, two groups compared the dNTP levels in the resting and activated CD4+ T cells and found that the resting CD4+ T cells exhibit much lower levels of dNTPs than the activated CD4+ T cells. However, in the presence of dNTPase SAMHD1, which has been identified as a HIV-1 restriction factor to limit HIV-1 reverse transcription, HIV-1 replication in the resting CD4+ T cells is significantly suppressed, suggesting that SAMHD1 acts as a HIV-1 restriction factor against HIV-1 in noncycling cells.50,61

**CONCLUSIONS**

HIV has evolved a diverse array of strategies to evade host immune responses, including those presented by the innate, adaptive, and intrinsic immune systems. NK cells, as the main component of the innate system, play an important role in combating HIV infection through cytolytic and noncytolytic mechanisms. However, HIV-1 employs different strategies to antagonize NK-mediated anti-HIV-1 activity, including selecting sequence polymorphisms within regions targeted by KIRs, using its Nef protein to down-regulate the expression of NKR ligands, or modulating NK cell differentiation and maturation. Complement is another component of innate immunity against HIV by mediating viral lysis. However, HIV can also use complement to attach to macrophages or dendritic cells that express complement receptors, thus enhancing HIV infection.

The humoral and cellular immune systems are the main
components of the acquired/adaptive immune systems. After infection, HIV can induce neutralizing antibody and CTL responses against the invading virus. However, the virus can quickly change its Env glycoprotein’s sequences to prevent recognition by neutralizing antibodies and CTLs. In addition, HIV can use its glycan shield to protect itself from antibody attack. HIV can also hide in the latent reservoir so that CTLs are unable to kill it.

The recent discovery of a series of anti-HIV restriction factors, such as APOBEC3G, TRIM5α, tetherin, and SAMHD1, gives some hope of developing these proteins as therapeutics for treatment of HIV infection. However, it has been quickly demonstrated that HIV has, again, evolved a variety of strategies to fight against intrinsic immunity, most notably by using some viral accessory proteins, such as Vif, Vpu, Nef, or Vpx, as antagonists of the above restriction factors.

Understanding the mechanisms of HIV immune evasion will allow us to develop novel strategies to prevent and cure HIV/AIDS. For example, we may design and develop artificial restriction factors with broader antiviral activity and higher resistance to the viral antagonists. These artificial host restriction factors may also be effective against viral pathogens.

REFERENCES


