Mechanism of Viral Immune Evasion

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Abstract. This article explores how viruses evade the host's immune system through various mechanisms. Initially, the article introduces the innate immune system as the first line of defense against pathogens, activating an immune response by recognizing pathogen-associated molecular patterns (PAMPs). However, viruses such as HIV-1, Ebola virus (EBOV), and members of the Herpesviridae family have developed complex strategies to circumvent these defense mechanisms.HIV-1 evades the immune system by integrating into the host genome to form latent infections, exhibiting high genetic variability, and through cell-to-cell transmission. Ebola virus suppresses the function of pattern recognition receptors (PRRs), such as RIG-I and MDA5, and interferes with signaling pathways through its VP35 and VP24 proteins, thereby inhibiting the production of interferons (IFNs). Members of the Herpesviridae family evade the host's innate immune response by interfering with PRRs, degrading immune factors, inducing post-translational modifications (PTMs), utilizing molecular sink strategies, and inhibiting the production of type I interferons and pro-inflammatory cytokines.The article emphasizes that a deep understanding of these viral immune evasion mechanisms is crucial for the development of effective antiviral therapies and vaccines.

Keywords: Acquired immunity; Innate immune system; HIV-1; Ebola; Alpha-herpesviruses; Immune evasion.

1. Introduction

In the long struggle between human and virus, the immune escape mechanism of virus has been a hot topic in medical research. Viruses, as a class of non-cellular organisms, rely on host cells to replicate and spread. In order to survive and reproduce, they have evolved multiple strategies to evade the host's immune system. These strategies are not only critical to the spread of the virus, but also have a profound impact on the severity of the disease and the difficulty of treating it. This article will explore how viruses evade innate and acquired host immune responses through various mechanisms, in particular immune escape strategies for pathogens such as HIV-1, Ebola virus, and herpes simplex virus. By gaining insight into how these viruses interact with the host immune system, we can provide a theoretical basis for the development of new therapeutic strategies and vaccines.

The innate immune system serves as a crucial first line of defense against invading pathogens by swiftly recognizing a variety of conserved microbial components, including viral RNAs. Upon detection of these components, it initiates an innate immune response aimed at limiting the spread of infection. Unlike the adaptive immune system, which generates highly specific responses to particular pathogens, the innate immune response is more generalized and acts quickly upon pathogen entry. This immediate response not only helps control infections but also signals for the activation of the adaptive immune system, which can more precisely eliminate infectious organisms.

Host cells identify pathogens through their recognition of pathogen-associated molecular patterns (PAMPs). These PAMPs are unique molecular signatures found on pathogens that signal their presence. Both non-immune cells, such as epithelial cells, and immune cells, like macrophages, possess germline-encoded receptors designed to detect these pathogenic markers. These specialized receptors are known as pattern-recognition receptors (PRRs).

PRRs play a vital role in the immune response by recognizing specific PAMPs, which include bacterial lipopolysaccharides, flagellin (a protein associated with bacterial motility), and various nucleic acids from bacteria or viruses. These receptors are strategically located on the cell surface as well as within the cytoplasm and endosomes, enabling them to detect pathogens at multiple sites.

When PRRs bind to their corresponding PAMPs, they activate intracellular signaling pathways that lead to the production of inflammatory cytokines, chemokines, and other immune mediators. This response not only helps contain the immediate threat posed by the infection but also enhances the recruitment and activation of other immune cells, creating a coordinated defense mechanism [1].

Acquired immunity, which comes into play after microorganisms evade the innate defenses such as physical barriers, phagocytes, and the complement system. This specificity of the immune response is crucial for recognizing and responding to particular antigens from previously encountered pathogens.

The immune response is initiated through the interaction of antigens with immune cells like macrophages and lymphocytes. Macrophages engulf the pathogen, present its antigens, which are then recognized specifically by T lymphocytes due to their unique surface receptors that are pre-committed to particular epitopes.

The immune response manifests in two primary forms: humoral immunity, which is characterized by the production of antibodies by B cells that circulate in the blood and lymph, and cell-mediated immunity, primarily mediated by T cells and phagocytes. The former neutralizes toxins and opsonizes pathogens, while the latter is essential for combating intracellular pathogens through the activation of cytotoxic T cells and regulatory T cells (As shown in figure 1).

Specific immunity is acquired either through natural infection, which can be either symptomatic or asymptomatic, or through artificial immunization, such as vaccination with antigens that stimulate a protective immune response without causing disease.

There are two types of acquired immunity: active and passive. Active acquired immunity occurs when an individual's immune system responds to a natural infection or vaccination, leading to the production of memory cells for long-lasting immunity. In contrast, passive acquired immunity is the temporary transfer of preformed antibodies from an immune to a non-immune individual, typically through immunoglobulins, serum, or lymphoid cells, and lacks the development of memory immunity [2].

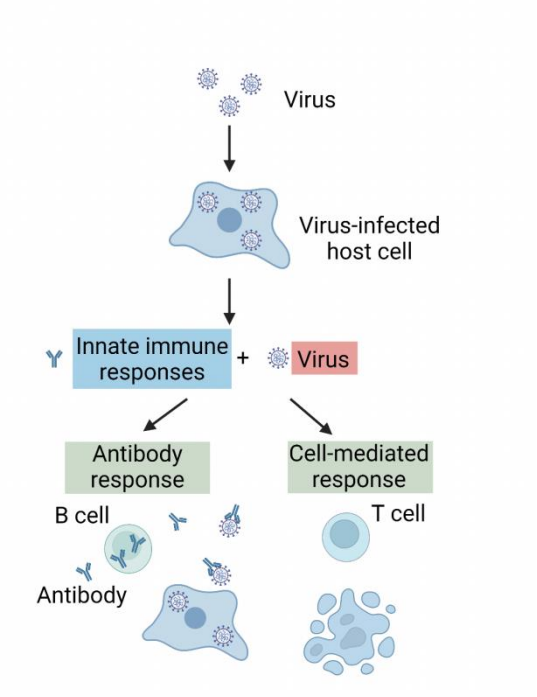

Fig. 1 The two main ways of immune responses [3].

2. Three Mechanisms of Viral Immune Evasion

This section explores three primary mechanisms through which viruses evade the host's immune system. The following paragraphs will discuss specific strategies employed by viruses such as HIV-

1, Ebola, and Alpha-herpesviruses, highlighting their complexity and effectiveness in immune evasion. Viruses like HIV-1, Ebola, and Alpha-herpesviruses employ distinct mechanisms to evade the host's immune system, enabling persistent infection and disease. HIV-1 evades immune detection through latent infection, high genetic variability, and cell-to-cell transmission. Ebola virus inhibits interferon responses by blocking pattern recognition receptors (PRRs) and counteracting host restriction factors, allowing it to suppress early antiviral defenses. Alpha-herpesviruses interfere with PRRs, degrade immune factors, and inhibit the production of interferons and pro-inflammatory cytokines. Understanding these immune evasion strategies is critical for developing effective antiviral therapies and vaccines, as it provides insight into how viruses circumvent host defenses. By targeting these evasion mechanisms, researchers can design treatments that enhance immune recognition, block viral replication, and ultimately prevent or control infections. Additionally, a deeper understanding of these processes can lead to the development of next-generation vaccines that prime the immune system to respond more effectively to these elusive pathogens, reducing the likelihood of chronic infection and disease progression.

2.1. HIV-1

HIV-1 employs various mechanisms to evade the human immune system. Firstly, the viral genome can integrate into the host cell's genome, establishing a latent infection that evades immune recognition and clearance. These latent infected cells can persist long-term, serving as reservoirs for the virus. Secondly, HIV-1 exhibits high genetic variability, making it difficult for the immune system to generate effective antibodies against all viral strains [4].

The viral surface is shielded by glycans, hindering neutralizing antibody binding and evading immune attack. Additionally, the envelope protein of HIV-1 can adopt a closed conformation, preventing vulnerable epitopes from being recognized by antibodies [4].

Furthermore, HIV-1 can evade immune attack through cell-to-cell transmission. This mode of transmission occurs through direct cell-to-cell contact or via virological synapses, which minimize viral exposure to antibodies and reduce the chances of immune clearance [4].

In summary, HIV-1 evades the human immune system through latent infection, genetic variability, and cell-to-cell transmission, making it challenging for the immune system to completely eliminate the virus [4] (as shown in figure 2).

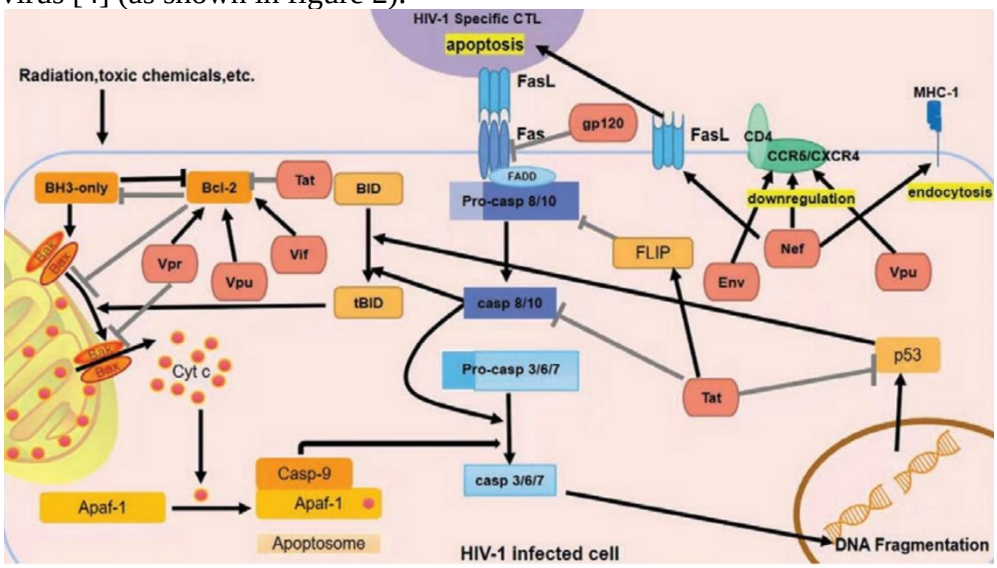

Fig. 2 HIV-1 escape mechanisms through apoptosis [3].

2.2. Ebola

Ebola virus disease (EVD) is a severe and frequently lethal disease caused by Ebola virus (EBOV). EVD outbreaks typically start from a single case of probable zoonotic transmission, followed by human-to-human transmission via direct contact or contact with infected bodily fluids or

contaminated fomites. EVD has a high case–fatality rate; it is characterized by fever, gastrointestinal signs and multiple organ dysfunction syndrome [5].

The Ebola virus has developed a sophisticated array of strategies to evade the host's innate immune system, which allows for its robust replication and contributes to its high pathogenicity. Key to these evasion tactics is the virus's ability to suppress the early antiviral response by inhibiting the function of pattern recognition receptors (PRRs) such as RIG-I and MDA5. This is achieved through the action of viral proteins like VP35, which interferes with the signaling pathways that would otherwise lead to the production of interferons (IFNs), a critical component of the antiviral state [6].

VP35, a multifunctional virulence factor, not only disrupts the interaction between cellular activators like PACT, RIG-I, and PKR but also acts as a 'decoy substrate' for kinases, preventing the activation of transcription factors necessary for IFN production. Furthermore, VP35 promotes the SUMOylation of IRF3 and IRF7, altering the signaling cascade and thus inhibiting IFN synthesis [6].

Ebola virus VP24 (eVP24) also plays a crucial role in immune evasion by blocking the nuclear translocation of the activated STAT1/2-IRF9 complex, a process essential for the induction of interferon-stimulated genes (ISGs). In Marburg virus, a close relative of Ebola, VP24 (mVP40) specifically inhibits the activation of JAK1, thereby preventing the signal transduction that leads to ISG synthesis [6].

In addition to these strategies, filoviruses have mechanisms to counteract the effects of ISGs produced in response to interferon signals, such as inhibiting the double-stranded RNA-dependent protein kinase PKR and the cellular restriction factor tetherin. The virus's glycoprotein may also play a role in evading tetherin's antiviral activity, potentially by facilitating the release of viral particles from infected cells [6].

Moreover, filoviruses subvert the cellular translation machinery by producing mRNAs with upstream open reading frames (uORFs) that can repress the translation of viral proteins, thereby possibly enhancing the survival of infected cells under stress. Marburg virus VP24 (mVP24) can interact with Keap1, modulating the cellular stress response and potentially increasing the survival of infected cells, although the exact contribution of this mechanism to viral survival has not been definitively proven [6].

In summary, the intricate immune evasion strategies employed by Ebola and related filoviruses at multiple levels of the host's immune signaling cascade underscore the need for a deeper understanding of these mechanisms to inform the development of effective antiviral therapies and vaccines [6].

2.3. Alpha-herpesviruses

The Herpesviridae family is classified into three subfamilies: alpha-herpesviruses, beta-herpesviruses, and gamma-herpesviruses subfamilies. All members of the Herpesviridae family establish latency, but the cells in which they establish latency vary. Most Alpha-herpesviruses establish latency in neurons [7].

Herpesviruses replicate in two ways: lytic replication and latent infection. During lytic replication, the virus enters a cell, and its DNA starts replicating once the capsid DNA is released into the nucleus. After assembly and genome packaging, the capsid exits the nucleus. The viral particles then undergo primary envelopment and de-envelopment at the nuclear envelope, followed by tegumentation and secondary envelopment in the cytoplasm. Finally, the virions exit the host cell via exocytosis [8].

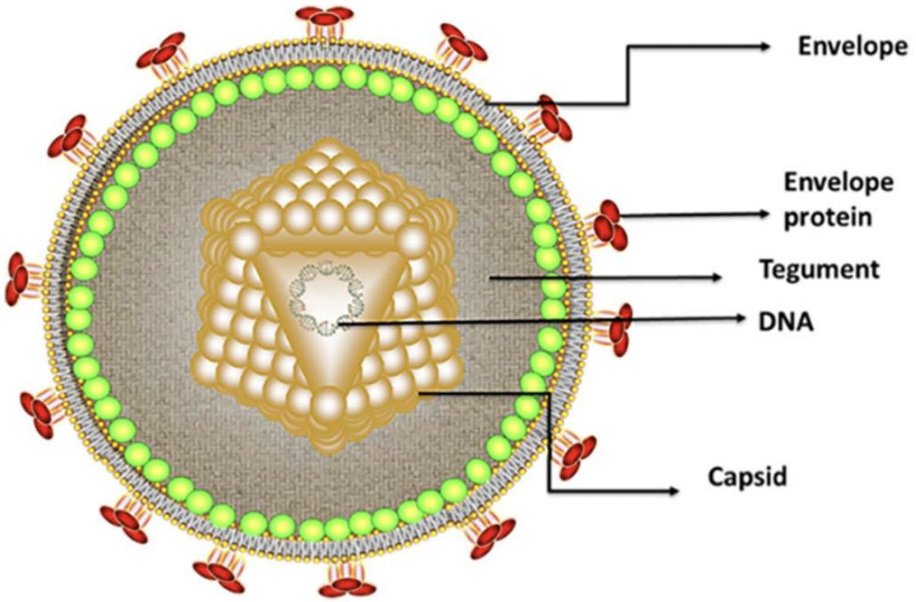

Fig 3 The structure of the herpes virus [9]

Herpesviruses are complex double-stranded DNA viruses, and their structure consists of several key components: first is the capsid, which is a protein shell made up of multiple identical protein subunits that are arranged in a specific symmetry to form a robust structure to protect the viral genetic material (as shown in figure 3). The genetic material is double-stranded DNA, which contains all the information needed for viral replication and infection of host cells. In some herpesviruses, the outer layer of the capsid is enveloped by a lipid envelope, which not only originates from the host cell but also aids in the spread of the virus within the host. The envelope is studded with various virus-encoded glycoproteins, which are crucial for the virus's recognition and fusion with host cells, and are key to the virus's entry into host cells. Between the capsid and the envelope, there is a loose structure composed of a variety of viral proteins, known as the tegument, which plays an important role in the assembly, maturation, and infection processes of the virus. The structure of the herpesvirus allows it to establish latent infections within the host and reactivate upon appropriate stimulation, leading to recurrent disease [9]. Alphaherpesviruses have evolved a multitude of strategies to evade the host's innate immune responses, ensuring their survival and propagation. These viruses can interfere with pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs), which are crucial for recognizing viral components (As shown in figure 4). For instance, they can block the activation of TLR2, which is involved in sensing viral glycoproteins, and TLR9, which detects viral DNA. Alphaherpesviruses also target specific PRRs; for example, herpes simplex virus (HSV) can degrade the DNA sensor IFI16 and inhibit the function of STING, a key adaptor protein in the cytosolic DNA sensing pathway [8].

Viruses in this family can degrade immune factors at both the mRNA and protein levels. The virion host shutoff (vhs) protein of HSV can destabilize and degrade host mRNA, including that of immune response genes, while viral proteins like ICP0 can promote the proteasomal degradation of key cellular factors such as MyD88, IRF3, and NF-κB. Additionally, they can induce post-translational modifications (PTMs) that inactivate immune signaling components, such as the deamidation of cGAS by pUL37 and hyperphosphorylation of IRF3 by pUS3, preventing their activation and downstream signaling [8].

Sequestration and molecular sink strategies are also employed, where viral proteins like VP22 and pUL46 bind to and neutralize immune factors, preventing their function in the immune response. Furthermore, alphaherpesviruses can inhibit the production of type I interferons (IFNs) and pro-

inflammatory cytokines by blocking the formation of inflammasomes and the activation of transcription factors like IRF3 and NF-κB [8].

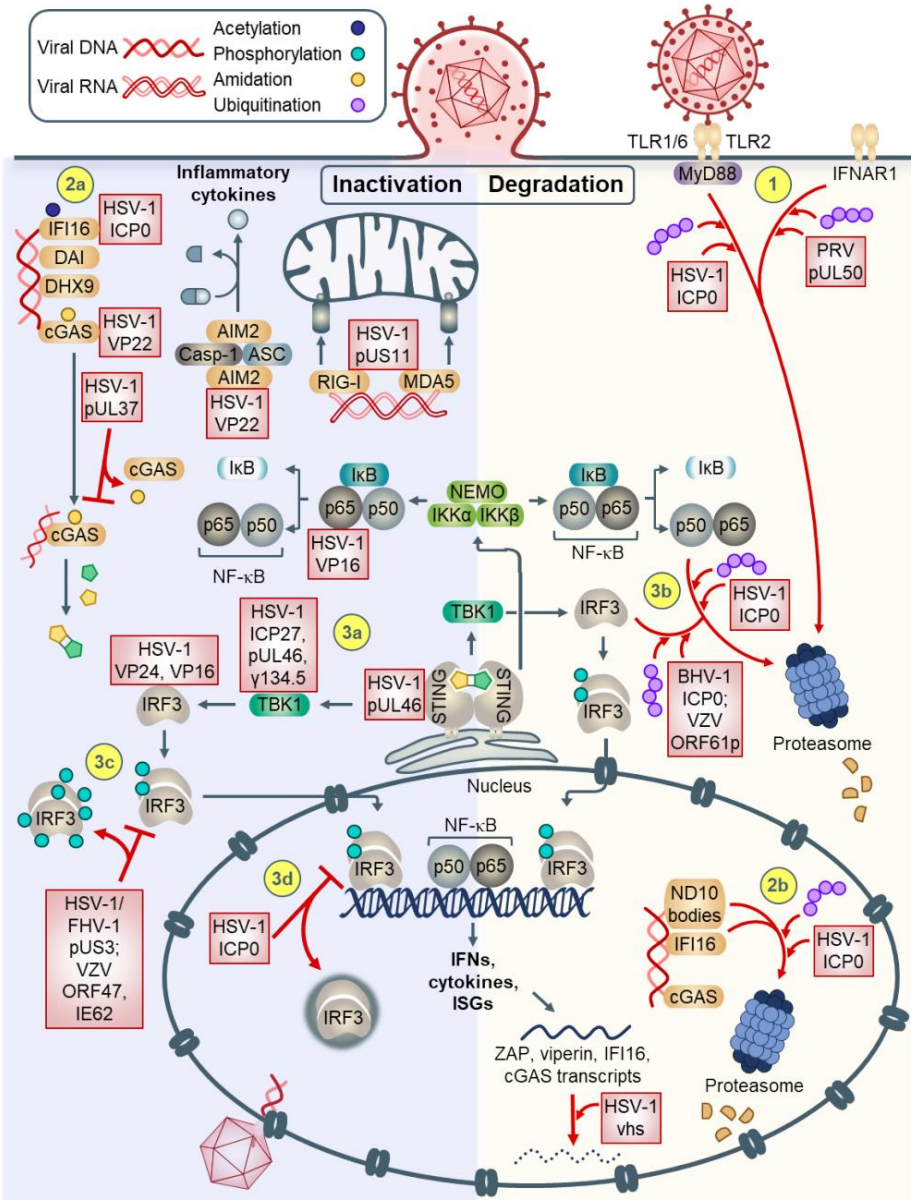

Fig. 4 Alphaherpesvirus evasion mechanism of innate immunity [8]

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