




REVIEW

Host–virus interaction and viral evasion

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Abstract

With each infectious pandemic or outbreak, the medical community feels the need to revisit basic concepts of immunology to understand and overcome the difficult times brought about by these infections. Regarding viruses, they have historically been responsible for many deaths, and such a peculiarity occurs because they are known to be obligate intracellular parasites that depend upon the host's cell machinery for their replication. Successful infection with the production of essential viral components requires constant viral evolution as a strategy to manipulate the cellular environment, including host internal factors, the host's nonspecific and adaptive immune responses to viruses, the metabolic and energetic state of the infected cell, and changes in the intracellular redox environment during the viral infection cycle. Based on this knowledge, it is fundamental to develop new therapeutic strategies for controlling viral dissemination, by means of antiviral therapies, vaccines, or antioxidants, or by targeting the inhibition or activation of cell signaling pathways or metabolic pathways that are altered during infection. The rapid recovery of altered cellular homeostasis during viral infection is still a major challenge. Here, we review the strategies by which viruses evade the host's immune response and potential tools used to develop more specific antiviral therapies to cure, control, or prevent viral diseases.

KEYWORDS

cytokines, immunity, immunology, interleukins, oxidative stress, viruses

1 | INTRODUCTION

Recent studies in the immunology field have described some factors that affect the quality and intensity of the host's immune response when it is exposed to infections. Among them, age, gender, genetics,

and comorbidities (Fink & Klein, 2015; Hooten & Evans, 2019; Martín et al., 2017; Yao et al., 2018), perinatal factors, and nutritional status (Alwarawrah et al., 2018; De Medeiros et al., 2018; Obanewa & Newell, 2017; Plaza-Díaz et al., 2018), environmental factors (Cannon et al., 2019), socioeconomic status (Meier et al., 2016), and

ABBREVIATIONS: APCs, antigen presenting cells; APOBEC3G, Apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like 3G; CCR5, C-C chemokine receptor type 5; CLR, C-type lectin receptors; CMV, cytomegalovirus; CTLs, cytotoxic T lymphocytes; DENV, Dengue virus; EBNA1, Epstein-Barr nuclear antigen 1; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HHV-8, herpesvirus type 8; HIV, human immunodeficiency virus; HSV-1, herpes simplex virus type 1; HTLV-1, T cell leukemia virus type 1; IFN, interferon type I; iNOS, inducible nitric oxide synthase; JEV, Japanese encephalitis virus; KSHV, Kaposi's sarcoma-associated Herpesvirus; LGP2, laboratory of genetics and physiology protein 2; LPS, lipopolysaccharides; MAVS, mitochondrial antiviral signaling protein; MCMV, murine cytomegalovirus; MDA5, melanoma differentiation-associated protein 5; MIP-1 α , macrophage inflammatory protein 1-alpha; MIP-1 β , macrophage inflammatory protein 1-beta; NK, natural killer cells; NLRs, nucleotide-binding oligomerization domain-like receptors; NLRs, nucleotide-binding oligomerization domain-like receptors; pDCs, plasmacytoid dendritic cells; PRR, pattern recognition receptor; RIG-I, retinoic acid-inducible gene-I; TLR, toll-like receptor; VSV, Indiana vesiculovirus; VV, Vaccinia virus; VZV, Varicella Zoster virus; WNV, West Nile virus.

immunological status may be determining factors for the establishment of a viral infection (Zimmermann & Curtis, 2019). The contribution of both viral and host factors determines vulnerability to viral infection and pathogenesis (Zimmermann & Curtis, 2019). The exact mechanisms of how these factors influence pathogenesis have fundamental importance for the development of infection prevention strategies.

For example, age can be a determining factor in the establishment of a viral infection. In newborns, the immune system is immature. This often represents a deficiency in immune responses, which predisposes these individuals to certain infections with higher pathogenicity. This is what happens when the hepatitis B virus (HBV) is acquired vertically, in toddlers or even children, being more likely to persist when compared to infection by this virus in adults (Zimmermann & Curtis, 2019). In addition, the humoral response of newborns is dependent on the vertical transmission of antibodies during pregnancy or breastfeeding (Letson et al., 2004; Vitorica et al., 2016).

Poor nutrition leads to global immunodeficiencies in children, adolescents, and the elderly. In 2016, an estimated 159 million children under the age of 5 years worldwide were seen to be wasted or severely wasted and suffered from stunting. In addition, around 45% of deaths among children under the age of 5 years were linked to undernutrition (World Health Organization, 2020). Moreover, the number of children suffering from malnutrition in West and Central Africa has increased at an alarming rate from 22.4 million to 29.0 million between 2000 and 2019 (UNICEF, 2020). There is a relationship between undernutrition and infection, with undernutrition compromising immune function or impairing an effective response (Calder & Jackson, 2000). Poor nutrition leads to a reduced innate immune response following stimulation of important receptors activated by viruses, such as the Toll-like receptor (TLR) superfamily (Djukic et al., 2014; Walker et al., 2011).

Genetic defects, such as mutations in nucleotide-binding oligomerization domain-like receptors (NLRs) belonging to the pattern recognition receptor (PRR) family (Kim et al., 2016; Kuenzel et al., 2010; Mortaz et al., 2017), can also contribute towards an ineffective immune response.

The host's first line of defense against a vast array of potentially pathogenic microorganisms, including viruses, is the skin and mucosa, which form part of the innate or nonspecific immune response (Bedecković et al., 2018; Coursaget, 2014). These anatomical barriers are equally as important as other components of the innate and adaptive immune responses. Local immunity then limits the spread of viruses from the focus of infection and also plays an important role in activation of the adaptive immune response (Carbone & Gebhardt, 2014; Desai et al., 2018).

Regarding immunological aspects, chemokines play an important role in the regulation of immune cell migration and activation, which is crucial for a comprehensive antiviral immune response (Alkhatib et al., 1996). Chemokines, such as those regulated on activation, normal T cell-expressed and secreted (RANTES) chemokine, macrophage inflammatory protein 1-alpha (MIP-1 α), and MIP 1-beta

(MIP-1 β), are important chemokines that act through C-C chemokine receptor type 5 (CCR5). This receptor is expressed on several immune effector cells such as natural killer (NK) cells, T cells, and macrophages (Alkhatib et al., 1996; Kou & Kuang, 2019).

During cell activation, viruses enter the cytoplasm and generate double-stranded RNA (dsRNA) during replication. The infected host cells can recognize such dsRNA and activate intrinsic antiviral signaling pathways with the production of interferon (IFN) type I, inducing multiple aspects of innate and adaptive responses (Yoneyama & Fujita, 2008). This process is mediated by cytosolic PRRs, such as retinoic acid-inducible gene-I (RIG-I), melanoma differentiation-associated protein 5 (MDA5), and laboratory of genetics and physiology protein 2 (LGP2), which are expressed in most cutaneous cell types and in remarkably high levels following exposure to IFN type I (Kawai & Akira, 2009).

The C-type lectin receptors (CLRs) expressed in cutaneous antigen-presenting cells (APCs) can also be mentioned in this context. These receptors mediate internalization of the viral ligand or of the virus itself in intracellular compartments, leading to their degradation and subsequent presentation of the antigen to APCs (Mercer & Greber, 2013; Sandgren et al., 2010). Upon viral activation, these receptors and transcription factors that induce the production of cytokines, such as IFN, interact as mediators of a direct antiviral response regulating multiple aspects of innate and adaptive immune responses.

Besides the above-mentioned mechanisms to decrease viral infection, we also can mention cell-mediated immunity factors related to macrophages, plasmacytoid dendritic cells (pDCs), and NK cells. Classically activated macrophages (M1-polarized macrophage subtype), when stimulated by IFN- γ or lipopolysaccharides (LPS), induce expression of the enzyme inducible nitric oxide synthase (iNOS or NOS2), which produces nitric oxide (NO) (Karupiah et al., 1993; Kobayashi, 2010; Martinez et al., 2006). Among the various physiological effects of NO, we can mention its antiviral effects against some viruses, such as Herpes simplex virus type 1 (HSV-1), Japanese encephalitis virus (JEV), and Dengue virus (DENV) (Croen, 1993; Neves-Souza et al., 2005; Saxena et al., 2000), among others. Concurrently, alternatively activated macrophages (M2-polarized macrophage subtype) are stimulated by cytokines and are found in high levels in human infections caused by the hepatitis C virus (HCV) and hepatitis B virus (HBV) (Saha et al., 2016; Tsai et al., 2018).

The importance of pDCs in the context of the innate immune response is that these cells express the TLR7 and TLR9 intracellular receptors, which recognize viral or microbial nucleic acids (Asselin-Paturel & Trinchieri, 2005; Y. Liu, 2005). This happens when pDCs secrete IFN type I, following activation of TLRs triggered by viruses or immune complexes (Cella et al., 1999).

Despite the restrictive factors mentioned above, almost all viral pathogens have developed mechanisms to inhibit the activation of complement system proteins (Lambris et al., 2008) by the production of molecules that bind to the Fc region of host immunoglobulins to prevent immunoglobulin G (IgG)-mediated virus neutralization (Lilley et al., 2001; Sprague et al., 2008) and the induction of

antibody-dependent activities against infected cells. The binding of antibodies to epitopes on the surface of infected cells results in activation of the complement pathway and cell lysis (Martinez et al., 2006; Van de Walle et al., 2003). Inhibition of its activation or binding to viruses ensures the development of a viral infection, as we will see in more detail throughout this review.

Within the context of the cellular immune response, the cytotoxic activity of peripheral NK cells occurs via its two major subtypes of CD56 surface molecules, which have different receptors and functional properties. The elevated and chronic production of some viruses may impede the immune response mediated by these cells, including affecting their interaction with dendritic cells and in some cases affecting their interaction with virus-specific cytotoxic T lymphocytes (CTLs). To escape the responses mediated by NK cells, viruses generally regulate the expression of HLA-A, B, and C types of MHC class I molecules (Gianchecchi et al., 2017).

The cellular immune response mediated by CD4+ and CD8+ T cells by the expression of MHC class II molecules on the surface of APCs is essential for the presentation of antigenic peptides foreign to CD4+ T cells. Viruses encode proteins that may interfere with the expression of MHC class II antigens by negatively regulating their transcription and/or disrupting their normal cell trafficking, interfering with their presentation to naive CD4+ T cells by disrupting the interaction between MHC class II antigens and TCRs. This is what occurs with the human immunodeficiency virus (HIV) proteins Tat and Nef, as described in more detail throughout this review (Cao et al., 2018; Rivino, 2018; Yee & Poh, 2018).

In the case of MHC class I expression by CD8+ T cells, IFN type I signaling, for example, specifically enhances the expression of MHC class I molecules and costimulatory molecules presented by APCs (Fitzgerald-Bocarsly, 1993; F. Zhou, 2009). Other cytokines produced by innate immunity cells reinforce the signaling mediated by IFN type I to ensure the expansion and function of cytotoxic CD8+ T cells. Therefore, in acute viral infections, most viruses are eliminated by CD8+ T cells, resulting in antigen depletion and establishment of CD8+ T cell memory.

In chronic viral infections, certain viruses can escape the host's immune responses, becoming latent and invisible to the immune system. Viruses such as HSV-1, Varicella-Zoster virus (VZV), cytomegalovirus (CMV), and HIV have developed latency that ensures maintenance of the viral genome with reduced viral gene expression and minimal activity, but at the same time persistently replicating in host cells, causing vigorous and sustained stimulation of TCRs and positive regulation of inhibitory receptors that lead to depletion of CD8+ T cell effectors. In the case of HIV, it is also known that persistent antigenic stimulation compromises the development of CD8+ T cell memory, allowing quiescent infection where the provirus is maintained as an integral part of the host genome with minimal viral replication (Grinde, 2013).

In addition to the inactivation of MHC class I and/or MHC class II receptors, the persistent activation of T cells induces an inflammatory condition (Belkaid & Rouse, 2005) that can lead to tissue

or systemic damage. Influenza virus infection may induce lung inflammation with massive tissue damage (Julkunen et al., 2000).

The coexistence of viruses and hosts imposes an evolutionary pressure on the immune system. As mentioned above, viruses can interfere with the functioning of the humoral and cellular immune responses by developing a series of immune evasion mechanisms enabling them to avoid being recognized by the host's immune system, for example by altering their immunodominant epitopes (epitope mutations), or, in the case of chronic viral infections, by becoming latent (McMichael et al., 2010).

Other mechanisms of viral evasion also include the inhibition of apoptosis by the virus-producing caspase inhibitors and virus tropism factors. The viruses encode viroins and viroreceptors that can act as mimetics or antagonists of their cellular counterparts, by altering signal transduction and cellular communication for survival of virus-infected cells (Shirogane et al., 2019; Vieyres & Pietschmann, 2019;). Tropism is determined by the presence of membrane receptors in host cells, which interact with viral proteins (antireceptors), allowing entry of the infectious agent into the cytoplasm, as occurs in human T cell leukemia virus type 1 (HTLV-1), HIV, Epstein-Barr virus (EBV) and Herpesvirus type 8 (HHV-8) infections (Inoue et al., 2003; Jones et al., 2011; Speck et al., 2000; Wilen et al., 2012). In addition to inhibiting apoptosis by means of the production of caspase inhibitors, viruses can hide viral protein-to-peptide processing that occurs in proteasomes present in the cytosol. For example, the Epstein-Barr nuclear antigen 1 (EBNA1) escapes CTL detection and encodes a mechanism to inhibit epitope generation (Levitskaya et al., 1997).

Some mechanisms have been suggested to explain the viral evasion of novel SARS-CoV-2, which involves CpG deficiency, 2'-O-methylation of viral RNA, viral suppressor RNAi, and the ORF8 and ORF3b proteins, which will be discussed further in this review.

Further to the various viral immune evasion mechanisms described above, understanding how viruses are capable of sequestering host cell metabolism, by inducing increased absorption and catabolism of nutrients in the host cell to support the production of new progeny, is an interesting challenge that could reveal how these evasion strategies or modulation of the host metabolism translate into the clinical outcome of the infection, or how current therapies could prevent the persistence of viral infection.

2 | FACTORS THAT INFLUENCE THE IMMUNE RESPONSE

The contribution of viral and host factors determines vulnerability to viral infection and pathogenesis. The exact mechanism of how these factors influence pathogenesis is of fundamental importance for the development of strategies to prevent infection.

There are some factors that affect the quality and intensity of the host's immune response when it is exposed to viral infections, as described below.

2.1 | Age

Age can be a determining factor in establishing a viral infection. In newborns, the immune system is not fully developed. The humoral response of newborns and toddlers relies on the passive transfer of maternal antibodies during pregnancy or breastfeeding. These antibodies influence the vaccination process as they act as neutralizers of the vaccine agent. Children are therefore vaccinated after 6 months of age, long enough to avoid interference of maternal antibodies (Jakaitis & Denning, 2014).

A lot of changes in innate and adaptive immunity are common in the aging population, reflecting a deterioration of the immune system and leading to terms such as “immune aging” or “immunosenescence.” Many markers of immunosenescence stem from the investigation of T and B cells, which show an altered pattern of cytokines, a decrease in clonal expansion and B cell and antigen-specific T cell function, and a decrease in the function of APCs. Decreased immunological functions lead to increased susceptibility of the elderly to viral, bacterial, and fungal infections, reactivation of pre-existing latent viruses, and a reduced response to vaccines (Franceschi et al., 2000; O'Connor et al., 2014).

In addition, metabolic dysfunction, impaired immune response to new antigens and inflammatory disorders are commonly found in the elderly and reflect a strong link between metabolic dysregulation and immune responses. Another example of this strong link is that several metabolic syndromes, especially obesity and diabetes, have inflammatory components (e.g., interleukin-6 and advanced glycation end products [AGEs] that trigger oxidative stress) and appear to be a driving force behind the pathogenicity of many viral infections (Franceschi et al., 2000; O'Connor et al., 2014).

2.2 | Genetic constitution

Chemokines such as RANTES, MIP-1 α , and MIP-1 β are important chemokines that act through CCR5 (Sanchooli et al., 2014), which is a member of the heterotrimeric G protein superfamily, and its activation results in the recruitment of proteins from cell signaling pathways, more specifically: Rho GTPase, PI3-Kinase, MAPK, JAK/STAT, and PKB (Sorce et al., 2011; Wong et al., 2001). The activation of these signaling pathways is implicated in the proliferation of immunological cells, the expression of inflammatory cytokines, activation of the immune system, and a protective response to viral infections such as Influenza, CMV, HSV-1, HSV-2, HBV, and HCV (Piguet & Trono, 2001). In contrast to the viruses mentioned above, for HIV, CCR5 is a coreceptor that facilitates entry into CD4+ T cells. A 32 base pair deletion (Δ 32) in exon 1 of the CCR5 gene, which is polymorphic in different ethnic and geographic populations, leads to dysfunction or a decline in expression, resulting in a negative correlation with the development of AIDS (Ioannidis & International Meta-Analysis of HIV Host Genetics, 2001).

The interactions between viral phenotypes, tropism, and the use of coreceptors, and how these influence HIV pathogenesis are

important topics in HIV research, especially after two cases of HIV being cured following a bone marrow transplant from a homozygous CCR5 Δ 32 donor (Brown, 2015; Gupta et al., 2020; Hütter et al., 2009; Symons et al., 2014).

2.3 | Nutritional and immunological status

Some micronutrients have a direct relationship with the formation of antibodies and development of the immune system:

- Vitamin A supplementation maintains intestinal integrity, reduces the incidence of respiratory tract infections, mortality from diarrhea, and increases immunity. Measles depletes host vitamin A levels, and for this reason, the measles vaccination often includes a high dose of vitamin A (Oliveira & Rondo, 2007).
- Vitamin E: The antioxidant action of vitamin E acts on the removal of free radicals and vitamin E supplementation improves immune function in the elderly. It induces cell division and the production of interleukins by naive T cells, but not by memory T cells (Glynn et al., 2007; Grodstein et al., 2003; Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds, 2000).
- Vitamin D supplementation is effective in boosting the immune response against SARS-CoV-2, Influenza, HIV, and DENV (Giraldo et al., 2018; Grant et al., 2020; Jiménez-Sousa et al., 2018).
- Zinc deficiency is implicated in reduced neutrophil and NK cell immunity, reduced complement system activity, a decrease in T and B cells, suppression of late hypersensitivity and cytotoxic activity, and also reduced antibody production (Sena & Pedrosa, 2005).
- Breastfeeding: Immune deficiency is partially offset by breastfeeding. Breast milk has large amounts of IgA, secreted lysozyme from macrophages, T and B cells that release IFN- γ , migration inhibitory factors, and monocyte chemotactic factors. Thus, breast milk actively boosts the immune system through the transfer of antibodies and lymphocytes (Palmeira & Carneiro-Sampaio, 2016).

3 | MECHANISMS OF NONSPECIFIC IMMUNE RESPONSE

3.1 | Anatomical barriers and surface secretions

The skin is the host's first line of defense against a vast array of potentially pathogenic microorganisms, including viruses. It maintains local immunity by limiting the spread of viruses from the focus of infection and plays an important role in activation of the adaptive immune response. It is composed of immature dendritic cells and Langerhans cells present in the epidermis, which capture antigens and then transport them to draining lymph nodes.

Of equal importance is the mucosal immune system, which counts on lymphocytes and accessory cells to capture the antigens acquired by the respiratory and gastrointestinal tract. Peyer's

plaques in the intestinal wall and the tonsils in the oropharynx are also tissues of the mucosal immune system (Kawamura et al., 2014).

3.2 | Intact immune receptors and their activation by viruses

3.2.1 | TREM-1

The TREM-1 receptor, belonging to the immunoglobulin variable domain receptor (IgV) superfamily, is activated by viruses. In the literature, studies have reported the activation and increase in expression of TREM-1, followed by its internalization in neutrophils, following interaction with Filovirus glycoproteins (Marburg and Ebola); and increased expression of TREM-1 in cells exposed to the HIV-1 gp41 protein and in the serum of patients infected by dengue in the early stages of infection (Roe et al., 2014).

3.2.2 | Toll-like receptors (TLRs)

TLRs are the best characterized among those that integrate the family of PRRs and participate in the recognition of viral components. TLRs contain extracellular leucine-rich repeats that mediate the recognition of their respective pathogen-associated molecular patterns (PAMPs).

Nucleic acids of RNA and DNA viruses, such as dsRNA, single-stranded RNA (ssRNA), and demethylated CpG rich motifs (CpGDNA), are considered to be PAMPs and can be recognized by TLRs 3, 7, 8, and 9, which are located in intracellular compartments, such as endosomes and the endoplasmic reticulum (Gantier, 2014). TLR3 recognizes dsRNA, TLR7 and TLR8 recognize ssRNA, and TLR9 recognizes demethylated CpG rich motifs. TLRs 1, 2, 4, 5, and 6 are located on the cell surface and primarily recognize components of the bacterial cell wall and viral particles. The specialty of TLRs is to promote the production of IFN type I and inflammatory cytokines, leading to antiviral immunity (Figure 1) (Collins & Mossman, 2014).

TLR2 can be stimulated by various skin-associated viruses, including HSV, VZV, EBV, human and murine cytomegalovirus (HCMV and MCMV), and measles virus. In many of these cases, viral stimulation of TLR2 results in activation of the AP-1 transcription factor, which contributes to the induction of proinflammatory cytokine expression (Boo & Yang, 2010).

Activation of TLR3 in Epstein-Barr infection contributes to the release of inflammatory cytokines and viral RNA from infected cells. Subsequently, the production of IFN type I and tumor necrosis factor α (TNF- α) occurs.

TLR4 may be activated by LPS derived from the membrane of Gram-negative bacteria, and also detects viral structural proteins and glycoproteins. The TLR4 receptor has altered expression after infection of human B cells by HCV (Boo & Yang, 2010).

TLR7 and TLR8 can be stimulated by Kaposi's sarcoma-associated Herpesvirus (KSHV), Vaccinia virus (VV), DENV, West Nile virus (WNV), Rotavirus, and HIV-1. TLR9 can be stimulated by all types of Herpes, VV, and HIV-1. These endosomal TLRs induce the expression of IFN type I in pDCs, which are considered the professional producers of IFN and are absent in normal skin but have been described in inflammatory skin disease lesions (Boo & Yang, 2010; Frazão et al., 2013; Kawai & Akira, 2008).

3.2.3 | APOBEC protein family

Apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like 3G (APOBEC3G or A3G) is a member of the APOBEC family of cytidine deaminases (Salter et al., 2016; H. C. Smith et al., 2012) that is expressed at varying levels in different cell types and is inducible by IFNs (Bonvin et al., 2006; Thielen et al., 2010). APOBEC3G is the main representative of the APOBEC family that has been shown to have antiviral activity against RNA and DNA viruses, such as HIV-1 and HBV, respectively. A3H haplotype II is another variant that has an expression that correlates with increased anti-HIV activity (Morse et al., 2017). Furthermore, A3B and A3F have been suggested to protect liver cells against HBV infection through their upregulation

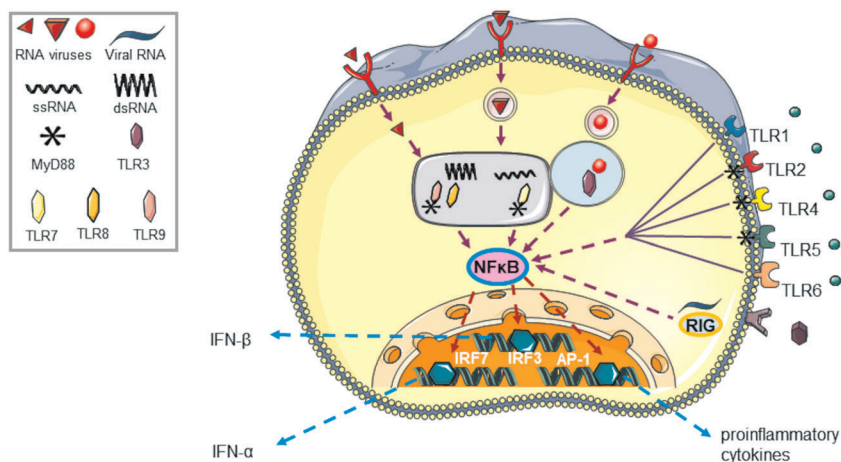


FIGURE 1 Representation of TLR activation by their respective PAMPs and the subsequent immune response. The rectangle in the upper left corner shows the PAMPs recognized by the intracellular TLRs 3, 7, 8, and 9. AP-1, activator protein 1; dsRNA, double-stranded RNA; IFN, interferon; IRF, interferon regulatory factor; MyD88, myeloid differentiation primary response 88 protein; NF- κ B, nuclear factor kappa B; RIG, retinoic acid-inducible gene; ssRNA, single-stranded RNA; TLR, Toll-like receptor

mediated by IFN- α (Bonvin et al., 2006). The antiviral effect of APOBEC3G has been explored in a broad range of retroviruses, including HIV-1, where the induction of G-to-A hypermutation in the nascent retroviral DNA of viral infectivity factor (Vif)-defective HIV-1 has been observed (Mangeat et al., 2003; H. Zhang et al., 2003). APOBEC3G can also bind to a retroviral RNA template or ssDNA and inhibit the viral reverse transcriptase (RT), leading to the production of nonviable viruses (Chemudupati et al., 2019).

3.2.4 | NOD-like receptors

Nucleotide-binding oligomerization domain-like receptors (NLRs) are PRRs that are involved in the recognition of viral PAMPs. NLRP3 is a receptor belonging to the subfamily of NLRs that encodes the NALP3 protein, which is involved in activation of the inflammasome (Durán et al., 2014).

3.2.5 | Retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs)

RLRs are cytosolic receptors consisting of RIG-I, MDA-5, and LGP2. They are expressed in most cutaneous cell types and are remarkably elevated following exposure to IFN type I after viral infection. RIG-I is preferentially involved in the detection of short dsRNA and staple RNA, whereas MDA-5 is more sensitive to long dsRNA. Recognition of viral RNA by RIG-I and/or MDA-5 triggers the production of IFN type I through the adapter protein called mitochondrial antiviral signaling protein (MAVS) and the transcription factors NF- κ B, IRF3, and IRF7. RIG-I is essential for immune defense against EBV, Measles, and HIV, while MDA-5 recognizes HSV and VV. Both RIG-I and MDA-5 are activated by DENV (Bruns et al., 2012; Chiang et al., 2014; Rodriguez et al., 2014).

3.2.6 | C-type lectin receptors (CLRs)

Most CLRs are expressed on cutaneous APCs, such as Langerhans cells, dendritic cells, and macrophages, and recognize mannose, fucose, and glycosylated structures of viruses (Bermejo-Jambrina et al., 2018). These receptors mediate internalization of the viral ligand or the virus itself into intracellular compartments, leading to their degradation and subsequent presentation of the antigen to APCs. CLRs activate distinct signaling pathways through kinases, such as spleen tyrosine kinase and Src kinase, which modulate the induction of specific cytokines (Lowell, 2011).

Most CLR studies are targeted at HIV-1. For HIV-1 infection, the virus needs to bind to CD4, and co-receptors (CCR5 or CXCR4) expressed on T cells and macrophages. In addition, HIV-1 can bind to different CLRs that are also expressed in these cells. There are two main mechanisms of transmission of HIV-1 between cells. The first of these mechanisms is a *cis* infection, where target cells are infected

with progeny virions via CD4 and coreceptors, and the viruses are released by productively infected cells (Coleman et al., 2013). The other mechanism consists of *trans*-infection, which occurs via a CLR-mediated immune synapse or exosomal pathway, where target cells are infected by virions that are captured by surrounding donor cells, and the viruses do not exhibit productive infection. CLRs of the DC-SIGN, MR, and CLEC4A types promote *cis*-infection by increasing interaction between the glycoprotein gp120 present in the HIV-1 envelope and CD4, but also facilitate viral capture and *trans*-infection in CD4⁺ T cells (Kawamura, 2016; Lambert et al., 2011).

3.3 | Production of IFN

All organisms have developed protection mechanisms against attack by pathogens. Mammals and other species have evolved to recognize conservative patterns of invading pathogens and produce IFN rapidly. The transcription factors IRF3 and IRF7 are important to produce IFN type I and controlling viral infections (Levy et al., 2011). These mediators show direct antiviral action and regulate multiple aspects of innate and adaptive immune responses. IFN type I, in addition to directly suppressing viral replication, also regulates the CD8⁺ T cell response. IRF3 is activated by recognizing PAMPs, such as nucleic acids or LPS. The RIG-I signaling pathways and TLRs and RLRs converge for the activation of IRF3. RIG-I and MDA-5 recognize RNA viruses that activate the adapter molecule IPS-1, which is required for the activation of IRF3, to promote the production of IFN type I. The rapid production of IFN induces hundreds of IFN-stimulated genes (ISGs) that function collectively to block all aspects of the virus life cycle. If viruses succeed in blocking IFN production, an innate IFN-independent response occurs. This response allows the cell to respond to stimuli involving low virus concentrations without the consequences that IFN could cause in the host, such as the infiltration of various cells of the immune system into the infected tissue or organ, which would lead to a marked inflammatory condition (Boo & Yang, 2010; Levy et al., 2011; Ysebrant de Lendonck et al., 2014).

3.4 | The complement system

Complement proteins are part of the innate immunity that provides the first line of defense against a wide variety of microorganisms. Almost all pathogens have developed mechanisms to inhibit the action of the complement, preventing its activation or attachment to the virus.

The classical pathway of the complement system eliminates infected cells by activating the complement cascade, resulting in the formation of pores in target cells. Host cells are protected against the action of the complement system by the expression of complement activation regulators (RCA) in their membranes. These RCAs negatively regulate complement activity, inhibiting the formation of C3 (C3 convertase) activation enzymes and preventing the formation

of the membrane attack complex (Pratheek et al., 2013; Ricklin, 2012).

3.5 | Macrophages and dendritic cells

Macrophages can adopt a variety of active phenotypes, depending on the cellular environment in which they are found. Classically activated macrophages (M1-polarized macrophage subtype), when stimulated by IFN- γ or LPS, induce expression of the enzyme inducible nitric oxide synthase (iNOS or NOS2), which produces NO (Figure 2a) (Buzzo et al., 2017). Evidence shows that DC glycolytic upregulation is controlled by two distinct pathways; an early burst of glycolysis that is NO-independent, and a sustained commitment to glycolysis in NO-producing DC subsets (Thwe & Amiel, 2017). NO is a short-lived gas molecule that causes both physiological and pathological effects. Among the various physiological effects of NO, we can mention the induction of death of intracellular pathogens, including viruses. NO causes antiviral effects against HSV-1, VV, Indiana vesiculovirus (VSV), JEV, and DENV, among others (Akaike & Maeda, 2000; Myint et al., 2014; Trotter et al., 2005).

This molecule is important in cells or tissues infected by certain viruses that reduce the expression of MHC class I and/or class II molecules. Its effect is independent of the immune recognition of infected cells through T cells. Studies in the literature have evaluated the effect of NO on infections caused by HCMV and DENV.

For example, recent studies have demonstrated that HCMV promotes the differentiation of a subset of specific monocytes. This differentiation induces activation of the cellular signal transducer and transcription activator 3 (STAT3) with consequent generation of high levels of NO, to silence the immediate transcription of HCMV and to promote viral latency. These results demonstrate that through activation of the STAT3-iNOS-NO axis, HCMV differentiates human hematopoietic progenitor cells into a subgroup of immunosuppressive monocytes that are long-lived due to viral latency (Zhu et al., 2018). Regarding the DENV infection, the replication of NO-sensitive DENV is inhibited by NO production leading to lower virus load and consequently milder dengue disease (dengue fever). However, NO-resistant DENV is virulent with a higher replication rate and stronger influence on host genetic response (involving cytokines/chemokines and the activation of T cells, B cells, platelets, and inflammatory cells) as compared to NO-susceptible DENV (Chaturvedi & Nagar, 2009).

Alternatively, activated macrophages (M2-polarized macrophage subtype) are stimulated by cytokines, such as IL-4 or IL-13, and express arginase 1 (Arg1), which hydrolyzes L-arginine to L-ornithine and urea (Atri et al., 2018; Briken & Mosser, 2011). These macrophages are found at high levels in human infections caused by the HCV, HBV, H5N1, and H1N1 viruses, and, consequently, produce substantial amounts of Arg1. The enhanced production of Arg1 is associated with viral persistence and progression of the immunopathology caused by these viruses (Figure 2a) (Burrack & Morrison, 2014).

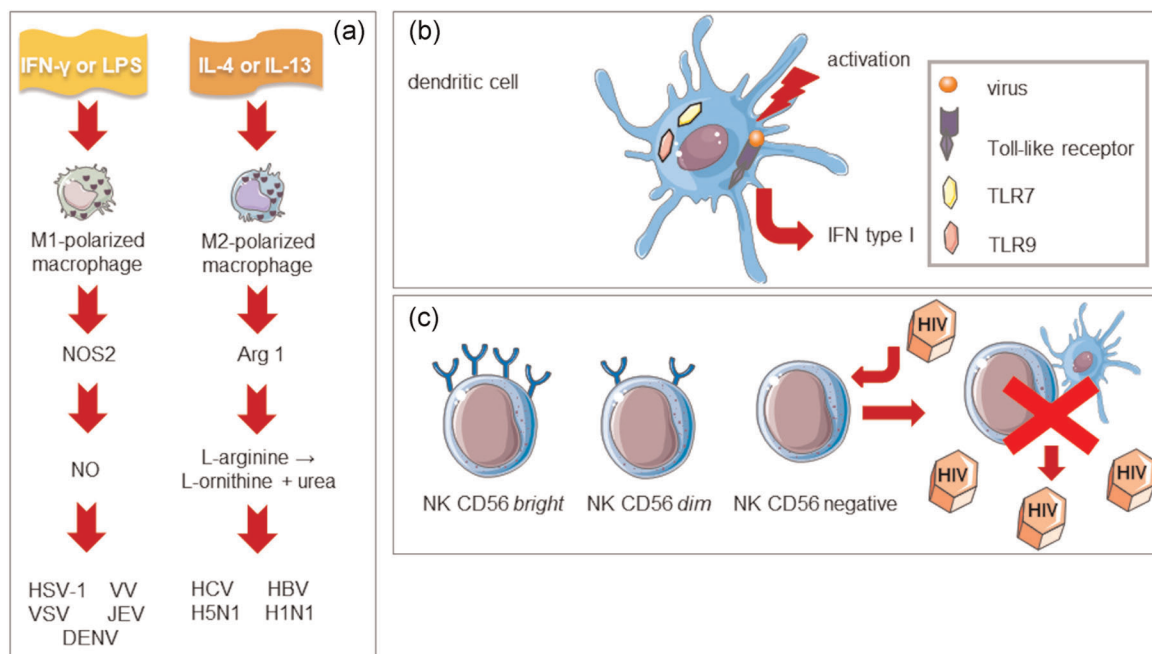


FIGURE 2 Mechanisms of nonspecific immune response mediated by cells. (a) M1-polarized macrophage subtype and M2-polarized macrophage subtype stimulation leading to distinct responses related to viral persistence and progression. (b) Dendritic cell response after activation of TLRs. (c) Deregulation of the interaction between NK cells and dendritic cells leading to viral disease progression. Arg1, arginase 1; DENV, dengue virus; H1N1, swine influenza virus A; H5N1, avian influenza virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus type 1; IFN, Interferon; IL, interleukin; JEV, japanese encephalitis virus; LPS, lipopolysaccharide; NK, natural killer cells; NO; nitric oxide; NOS2, nitric oxide synthase 2; VSV, Indiana vesiculovirus; VV, vaccinia virus

pDCs are APCs specialized in secreting IFN type I through the activation of TLRs, triggered by viruses or immune complexes. They express the TLR7 and TLR9 intracellular receptors, which recognize viral or microbial nucleic acids (Figure 2b) (Reizis et al., 2011; Simpson et al., 2016).

3.6 | NK cells

NK cells exhibit cytotoxic activity and induce the release of the cytokines IFN- γ , TNF, GM-CSF, and the chemokines CCL3/MIP1- α , CCL4/MIP1- β , and CCL5/RANTES upon activation of these cells by the virus. Peripheral NK cells have on their surface two major subtypes of the CD56 molecule, called CD56 bright (light, bright, or luminous) and CD56 dim (murky and dark), which have distinct receptors and functional properties. There is also a subtype detected at a low frequency in healthy individuals, called CD56 neg (negative). The latter circulates in large quantities in HIV-1 infected individuals. Although NK cells are not infected by HIV-1, high and chronic virus production impedes the immune response mediated by these cells, including their interaction with dendritic cells that are responsible for presenting HIV-1 antigens to T cells (Figure 2c) (Lugli et al., 2014). The deregulation of the interaction between NK cells and dendritic cells contributes to the spread of the virus to secondary lymphoid organs, thereby facilitating disease progression. HCV, HCMV, Hantavirus, and EBV also stimulate increased circulating levels of CD56 neg NK cells in the host (Pollmann et al., 2017).

4 | MECHANISMS OF ACQUIRED IMMUNE RESPONSE

4.1 | Humoral immune response

Antibodies and peptides of the complement system are essential for the elimination or neutralization of viral particles. They act by inhibiting the entry of viruses into the host cell, prevent their spread in the body, and act to prevent reinfections as we shall see below.

Antibodies efficiently neutralize viral antigens. The upper airways have large amounts of IgA and IgM, which neutralize respiratory viruses such as influenza (Figure 3a). The production of IgM occurs early during the immune response and precedes development of the response mediated by the class exchange of IgG and IgA immunoglobulins as a result of infection or vaccination (Figure 3a) (Baumgarth, 2013).

Only influenza A and B cause outbreaks of pandemics and severe disease (Couch & Kasel, 1983). These viruses have two surface antigenic proteins; hemagglutinin (HA or H) and neuraminidase (NA or N), with 16 subtypes of HA and 9 of NA having been described (Fouchier et al., 2005). Antigenic drift occurs as a result of point mutations in influenza A and B viruses and causes small, gradually accumulating changes in the structure of HA and NA. Antigenic drift in influenza A viruses is associated with a positive selection of spontaneous mutants with neutralizing antibodies (Bush et al., 1999). Such variants of the virus are no longer neutralized by antibodies, in contrast to the original viruses. Antigenic drift is observed among

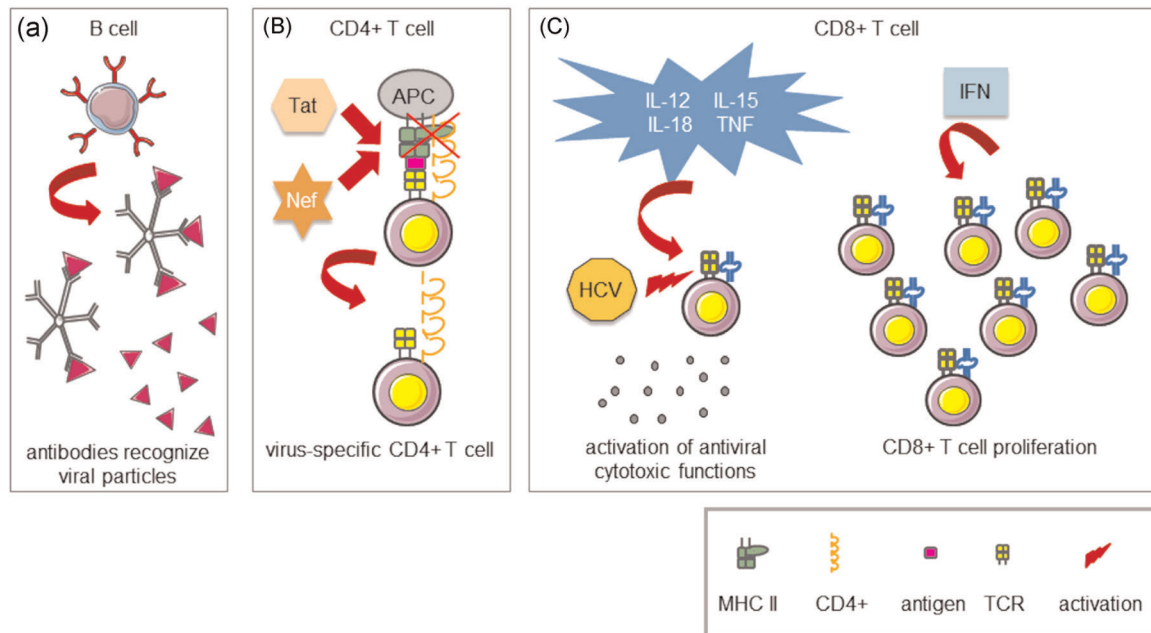


FIGURE 3 Mechanisms of an acquired immune response against viruses. (a) Antibodies produced by B cells neutralize viral antigens. (b) The HIV-1 Tat and Nef proteins interfere with MHC class II molecules, and as a consequence disrupt the generation of virus-specific CD4+ T cells essential to an effective antiviral immune response. (c) Specific cytokines stimulate the CD8+ T cell-mediated response. HCV chronic infection causes sustained stimulation of TCR and positive regulation of inhibitory receptors that lead to the depletion of CD8+ T cell effectors. APC, antigen-presenting cell; HCV, hepatitis C virus; Nef, negative regulatory factor; Tat, trans-activator of transcription

poultry viruses and is less pronounced in viruses that infect humans. Mutations in the nucleotide sequences of the HA and NA segments of human viruses occur with a frequency of less than 1% per year. However, it has been shown that single point mutations in one of the antigenic HA sites may be sufficient for antigenic variations (Wiley & Skehel, 1987). As a result of the emergence of the A/California/04/2009 (or A(H1N1) pdm09) pandemic strain in 2009, which differed in antigenic properties from all previous H1 serotype strains, the current H1 component became part of the current vaccines. In addition to hemagglutinin, antigenic drift has also been observed for neuraminidase and correlates with amino acid changes (Colman & Ward, 1985). The antigenic shift includes major antigenic changes, as a result of which HA and NA become different from circulating variants and enter the human population. Typically, this generates new subtypes of the virus, which have not yet circulated among people, before the appearance of a pandemic. These newly formed proteins are immunogenically different from those in previously circulating strains and cause a high infectious level of new viruses in naive populations, leading to a pandemic (Trifonov et al., 2009).

4.2 | Cellular immune response

Among the cellular immune responses, we can highlight those mediated by CD4+ and CD8+ T cells.

4.2.1 | CD4+ T cells

Expression of MHC class II molecules on the surface of APCs is essential for the presentation of antigenic peptides foreign to CD4+ T cells. Inhibition of virus-induced MHC class II antigen presentation interferes in the generation of virus-specific CD4+ T cells, and consequently, in the induction of an effective antiviral immune response. Viruses encode proteins that may interfere in the expression of MHC class II antigens by negatively regulating their transcription and/or disrupting their normal cell trafficking, interfering with their presentation to naive CD4+ T cells by disrupting the interaction between MHC class II antigens and TCR (Su & Davis, 2013).

The HIV-1 Tat protein competes with the transcriptional MHC class II transcriptant (CIITA) at the transcriptional level and represses the expression of genes encoding MHC class II antigens. Another way to subvert antigen presentation is by altering the intracellular trafficking of class II antigens. HIV Nef protein causes decreased expression of mature MHC class II molecules and increased expression of immature MHC class II molecules on the plasma membrane surface of CD4+ T cells (Figure 3b) (Dalrymple & Mackow, 2014).

4.2.2 | CD8+ T cells

CD8+ T cells are essential for the effective control of most viral infections. The initiation and expansion of the CD8+ T cell-mediated

antiviral response are largely dependent on the innate immune response. The latter is rapidly triggered and promotes the link between various PRRs and viral products.

IFN type I signaling specifically enhances the expression of MHC class I molecules and costimulatory molecules present in APCs. IFN can also act directly on increasing the proliferation of CD8+ T cells. Other cytokines produced by innate immunity cells reinforce signaling mediated by IFN type I to ensure the expansion and function of cytotoxic CD8+ T cells (Mescher et al., 2006). IL-12 produced by macrophages and dendritic cells induces the expression of T-bet transcription factor (T-box expressed on T cells) (Joshi et al., 2007). Induction of T-bet expression in CD8+ T cells is essential for the generation of cytotoxic antiviral effector functions (Singh et al., 2017). Other cytokines expressed by innate immunity cells, such as TNF, IL-15, and IL-18 also stimulate the CD8+ T cell-mediated response (Figure 3c) (N. Zhang & Bevan, 2011).

In acute infection, most viruses are eliminated by CD8+ T cells, resulting in antigen depletion and CD8+ T cell memory development, which can be long lasting and mediate rapid and effective responses to subsequent viral exposure.

In a chronic viral infection, CD8+ T cell specificity is determined by the nature of the infection itself. Certain viruses have developed latency that ensures maintenance of the viral genome with reduced viral gene expression and minimal active viral replication (Allen et al., 2011). This quiescent colonization of the host is associated with very low levels of viral antigens, appropriate development of T-cell memory, and maintenance of CD8+ T cell effectors that are stimulated by occasional expression of the viral antigen as a result of reactivation of the virus (Abbott et al., 2013). In contrast, HCV has active replication throughout its life cycle. This persistent replication in a host with chronic infection causes vigorous and sustained stimulation of TCR and positive regulation of inhibitory receptors that lead to the depletion of CD8+ T cell effectors, which is characterized by decreased cytokine production, attenuated proliferation, and apoptosis (Dustin, 2017; Naseem et al., 2018) (Figure 3c). In addition, antigenic and persistent stimulation compromises the development of CD8+ T cell memory (Naseem et al., 2018; Urbani et al., 2002). HIV virus has both quiescent and persistent life cycles. It can establish quiescent infection where the provirus is kept as an integral part of the host genome with minimal viral replication (Bradley et al., 2018). Quiescent infection, prevalent in HIV patients treated with antiviral therapy, occurs when infected CD4+ T cells are able to differentiate into memory cells that do not allow viral replication, and thus a stable reservoir of latent HIV is created (Bradley et al., 2018). On the other hand, in the absence of antiviral therapy, there is persistent replication of HIV, chronic stimulation, and CD8+ T cell depletion (Kulinski et al., 2013).

4.2.3 | Mechanisms of tissue aggression mediated by cellular immune responses

Activated T cells promote an inflammatory condition that can lead to tissue or systemic damage. Influenza virus infection, for example,

induces lung inflammation with massive tissue damage (Lê et al., 2015). CD4+ and CD8+ T cells use multiple regulatory mechanisms to eliminate virus-infected cells and reduce lung inflammation and injury (Vasileiou et al., 2020). In addition to the production of proinflammatory cytokines by activated T cells, we can cite “original antigenic sin” or “negative antigenic interaction” (Monto et al., 2017), which is defined by the tendency of the immune system to utilize immune memory based on the first infection, when a second, slightly different infection attempts to establish itself. Original antigenic sin is particularly harmful in influenza virus infections, dengue, and vaccinations. In the case of dengue, CD4+ and CD8+ T cell activation will be more potent in the secondary infection, resulting in a worse clinical condition compared to the traditional fever. This is because of the release of the cytokines IFN- γ and TNF- α , which can act directly in endothelial cells, promoting vascular injury and contributing towards plasma extravasation and the pathogenesis of hemorrhagic dengue (Dalrymple & Mackow, 2014). In the case of vaccinations, viruses can undergo antigenic variation, where their epitopes are altered through natural mutations, allowing them to escape the immune system. When this occurs, the mutated virus reactivates previously activated memory B cells, which produce antibodies. However, these antibodies associate inefficiently with the altered epitopes. There will therefore be no activation of naive B cells capable of creating new antibodies against this viral strain. The consequence is a less efficient immune response than the previous ones and with a longer course of infection (Dalrymple & Mackow, 2014).

5 | MECHANISMS OF IMMUNE SYSTEM EVASION

The coexistence of viruses and hosts imposes evolutionary pressure on the immune system. The host has developed an immune system that can respond to viruses and cells infected by them (H.K. Lee & Iwasaki, 2008; Seth et al., 2006). On the other hand, viruses have developed several immune evasion mechanisms to escape the host's immune system (Alcami & Koszinowski, 2000). Generally, the larger the viral genome, the more diverse the mechanisms used to extend the time of viral replication and the spread of viral particles.

Various mechanisms of evasion enable viruses to avoid recognition by the host's humoral immune response (Alcami & Koszinowski, 2000; Medzhitov, 2007). These mechanisms include altering immunodominant epitopes; interfering with the cellular immune response, for example, by disabling peptide presentation or affecting the performance of NK cells; and interfering with immune effector functions, for example, by affecting the expression of cytokines or blocking apoptosis, which are discussed below.

5.1 | Evasion of the immune response through latency

In Section 4.2.2 we briefly described the role of CD8+ T cells in chronic viral infections and the influence these cells have on viral

latency. As mentioned, the reversible state of a nonproductive viral infection in host cells is called latency. Viruses can elude the host's immune responses, becoming latent and invisible to the immune system (Wiertz et al., 1997). During latency, viruses can infect non-permissive or semipermissive host cells and persist in “immune privileged” tissues, such as the brain, retina, and kidney. This occurs with HSV-1, which infects and replicates in epithelial cells but can also persist in the form of latent infection, with low viral gene expression in sensory neurons of triplet ganglia that do not express MHC antigens (Garber et al., 1997; T. Liu et al., 2000). After certain stimuli, such as immunosuppression, trauma, exposure to sunlight or ultraviolet radiation, the virus can be activated and migrate through the axons of the neurons and infect epithelial cells. In the same way, VZV becomes latent in the dorsal root ganglia of the spinal cord (Gilden et al., 2011). CMV persists for a long time in the kidneys (Holma et al., 2000), retina (Voigt et al., 2018), and bone marrow (Bhat et al., 2015). HIV-1 is known to persist in the form of the transcriptionally inactive provirus in the CD4+ T cell genome of the host's memory cells for long periods (Gilden et al., 2011; Lungu et al., 1995). These cells lack the necessary transcription factors for the virus to replicate. Thus, the virus can remain in the brain, where it is protected by the blood–brain barrier against lymphocyte infiltration. These cells and tissues serve as reservoirs for viruses, which are resistant to therapy and pose a real challenge for complete elimination in the infected host.

5.2 | Epitope mutations

Virus-infected cells are normally recognized and eliminated by the immune system. One of the key steps to this is the presentation of viral peptides to MHC class I proteins, allowing the infected cells to be detected and killed by CTLs. In the case of HIV, this process works well, but only temporarily. A strong CTL response can be detected early after infection with a 1%–5% increase in the number of CD8+ T cells (Perreau et al., 2013), and is responsible for the abrupt decrease in plasma viremia after a few weeks of infection. HIV progressively destroys a range of T helper (Th) cells, thus preventing both the efficient production of antibodies by B cells and the adequate function of CTLs. HIV accumulates mutations in epitopes important for antibody-mediated neutralization or CTL recognition. Thus, if they “hide” in cells that are inaccessible to CTLs, they induce negative regulation of MHC class I or positive regulation of Fas on the surface of infected CD4+ T cells (Iannello et al., 2006; Piguet & Trono, 2001).

5.3 | Inhibition or induction of apoptosis

Apoptosis is a normal event in the maturation of B and T cells, and in the effector function of these cells in killing infected cells. Viruses have several distinct strategies to prevent the death of infected host cells, including the production of caspase inhibitors (proteases that

cleave cellular proteins), homologues of Bcl-2 (apoptosis inhibitory proteins), and FLICE-like inhibitory proteins (FLIPs). Cellular FLIPs are highly expressed in tumor cells, T cells, and myocytes, highlighting the critical role of FLIPs as endogenous modulators of apoptosis. Its viral counterparts, v-FLIPs, are encoded by various γ -herpesviruses (KSHV/HHV-8 and HVS) and human tumorigenic molluscipoxvirus (Senkevich et al., 1996). All γ -herpesvirus encoding FLIPs also encode a Bcl-2 homologue, which provides two complementary antiapoptotic functions (Hu & Usherwood, 2014). Thus, FLIPs facilitate viral propagation and persistence and contribute to the transforming capabilities of some herpes viruses. In addition to the production of FLIPs, viruses can also interfere in cell death signaling at a receptor level (Irmeler et al., 1997; Nagata, 1997). As an example, we can mention the Adenoviral E3-10.4/14.5 K protein that triggers the internalization of Fas (cell death receptor) present on the surface of infected cells and its destruction in lysosomes (Irmeler et al., 1997). As another example of the induction of apoptosis, we can mention IL-24, which is associated with apoptosis in tumor cells (Shisler et al., 1997) and infections caused by Influenza A (Seong et al., 2016; Weiss et al., 2015) and HIV-1 (Strumillo et al., 2019). Induction of apoptosis in infected cells would function as an antiviral mechanism, blocking the spread of viral progeny.

5.4 | Viral tropism and activation of immune system cells

Viral tropism is the tendency that a virus has in infecting a particular cell or tissue type. Tropism is determined by the presence of membrane receptors in host cells, which interact with viral proteins (antireceptors), allowing entry of the infectious agent into the cytoplasm of the cell (Brown, 2015; Piguet & Trono, 2001; Sanchooli et al., 2014).

The hypervariable region number 3 of HIV gp120 associates with the cellular chemokine receptor CXCR4 or CCR5. Different variants of HIV use one or the other receptor. The viral variant R5 uses the CCR5 receptor and the X4 variant uses the CXCR4 receptor. Throughout the infection, R5 variants can mutate and switch to the CXCR4 receptor (Figure 4) (Terahara et al., 2019; S. Zhou et al., 2016).

Another retrovirus, HTLV-1, also has a tropism for T cells. The HTLV-1 Tax protein is responsible for cell transformation as a result of its interaction with cellular transcription factors, such as NF- κ B, resulting in its permanent activation, providing growth of lymphocytes independently of IL-2 (Tagaya et al., 2019).

In addition to HTLV-1, EBV and HHV-8 (herpesviruses associated with Kaposi's sarcoma) also present sites of association with NF- κ B and its promoters (Keller et al., 2006), resulting in sustained activation and inducing cell transformation. EBV has a tropism for epithelial cells and B cells (Borza & Hutt-Fletcher, 2002), and is capable of inducing tumors and lymphomas. The EBV LMP-1 protein mimics the activated CD40 receptor (Gires et al., 1997; Kilger et al., 1998), which promotes the survival, proliferation, and expression of infected B cells.

5.5 | Virokines

During evolution, viruses have captured a wide range of cellular genes involved in immune recognition and cell growth control for their efficient viral replication. Virokines and viroreceptors encoded by viruses may act as mimetics or antagonists of their cellular counterparts, by altering signal transduction and cellular communication for survival of virus-infected cells.

After mapping the VV genome in the 1980s, the first viral encoded proteins secreted from infected host cells were discovered,

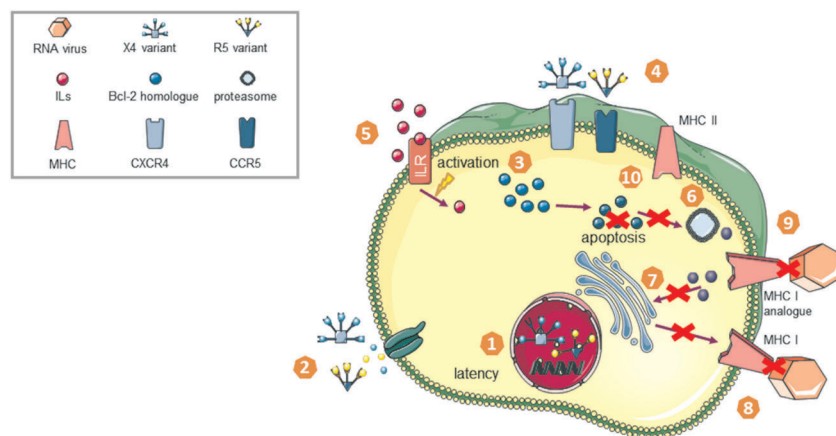


FIGURE 4 Mechanisms underlying strategies of viral evasion from the immune response. The rectangle in the upper left corner shows the receptors and their ligands involved in various strategies of viral escape. Numbers show: (1) Latent HIV-1 infection; (2) gp120 epitope mutation; (3) Bcl homologue production; (4) gp120 association with CXCR4 or CCR5; (5) ILs binding ILR; (6) Inhibition of proteasomal degradation; (7) TAP-mediated transport blockade (8,9) Inhibition of presentation by MHC class I and its analogues; (10) Inhibition of apoptosis by Bcl homologues. Bcl-2, B-cell lymphoma 2; CCR5, C-C chemokine receptor type 5; CXCR4, C-X-C chemokine receptor type 4; ILR, interleukin receptor

and the term *virokine* was coined (Kotwal & Moss, 1988) for such immunomodulatory molecules as viral homologs of cytokines. Another term coined was *viroceptors* for viral homologs of cytokine receptors, produced and secreted by virus-infected cells. Since then, many research studies have been dedicated to exploring their potential use as therapeutic agents showing the potential implications for viral epidemiology, treatment or prevention of viral and inflammatory diseases, and for the development of safer vaccines (Kontsek & Kontsekova, 2000). Many of these proteins are being investigated for use as novel therapeutic immunomodulators to manage immune disorders, inflammation after trauma, graft rejection, and autoimmune diseases (S. A. Smith & Kotwal, 2001). Also, these viral elements, which induce or subvert the host's cytokine responses against viral infection, may contribute to a better understanding of the mechanisms which help the viruses escape immune surveillance. Virokines and viroceptors are encoded by large DNA viruses such as herpesviruses and poxviruses. HHV8 is associated with Kaposi's sarcoma and lymphoproliferative diseases, such as lymphomas, pleural effusion, and Castleman's disease. HHV8 has a unique number of cellular regulatory genes, which redirect gene expression and cell growth, prevent apoptosis and immunological recognition, and also interfere with the function of the tumor suppressor gene. In addition, it encodes a single virokine, viral IL-6, which is particularly relevant in the pathogenesis of HHV8-associated tumors by participating in the mitogenic and proinflammatory effects of paracrine and autocrine pathways. Viral IL-6 differs from human IL-6 in receptor binding for signal transduction and thus constitutes a unique model for understanding the biology of human and viral cytokines (Klouche et al., 2004).

5.6 | Modulation in the process of antigen presentation

The peptides that are presented to MHC class I molecules result from the degradation of viral proteins by proteasomes in the cytosol. The degradation by proteasomes is dependent on the proteolytic cleavage of specific sequences within the protein. After fragmentation of the antigens by the proteasome, the resulting peptides are translocated from the plasma membrane into the endoplasmic reticulum (ER) through the transporter associated with antigen processing (TAP). The peptides carried by TAP are anchored to MHC class I (Hengel et al., 1997). Viruses can escape the processing of these proteins into peptides by altering parts of their genome, via viral proteins. EBV encodes the Epstein-Barr nuclear antigen 1 (EBNA1), escaping detection by CTLs, and encodes a mechanism to inhibit epitope generation (Levitskaya et al., 1995). HCMV expresses the US6 protein in the initial phase of infection, which inhibits TAP, and its presence in the late phase of viral replication limits the presentation of structural viral antigens such as glycoprotein B. HSV 1 and 2 encode the cytoplasmic protein ICP47, which obstructs the peptide binding site in TAP, thereby blocking the presentation of viral peptides to MHC class I (Ahn et al., 1996; Androlewicz et al., 1993; Iannello et al., 2006).

5.7 | Evasion of NK cell-mediated cytotoxicity

NK cells are generally activated in the early stages of a viral infection, before generation of virus-specific antibodies and CTLs. This shows their important role in controlling viral replication. However, some viruses, particularly HIV-1, have developed multiple strategies to escape NK-mediated immune response.

The most important ligand recognized by NK cells is the human leukocyte antigen class I (HLA class I), particularly A and B types, encoded by the MHC class I gene complex. The peptide repertoire presented by HLA class I changes during viral infection, resulting in elimination of the infected cell by NK cells. Thus, normally, viruses down-regulate HLA-A and B expression on the surface of infected cells to escape the antiviral response (Mwimanzi et al., 2017). On the other hand, HLA-C and E act primarily as ligands for inhibitory Killer-cell immunoglobulin-like receptors (KIRs) on the surface of NK cells. Viruses can evade NK-cell responses by increasing HLA-E expression. To achieve this, such a nonclassical HLA molecule needs peptides derived from HLA-G signal sequences and many HLA-A, B, and C alleles (Rölle et al., 2018).

Moreover, the expression of some viral sequence variations can also lead to engagement of KIRs for resistance of viruses to NK cells. At least one HLA-presented immunodominant epitope derived from HIV p24 protein associated with HLA-E has been identified that allows engagement of KIRs to inhibit NK cell function (Fadda et al., 2012) by increasing the expression of this antigen on the surface of virus-infected cells (Sharpe et al., 2019). The epitopes derived from HCMV glycoprotein UL40, presented to NK cells by HLA-E molecules via CD94/NKG2A receptor also protect infected cells from NK cell-mediated killing (Heatley et al., 2013).

The presence of HLA class I antigens on the surface of infected cells and the natural selection of viral epitope variations provide novel opportunities for viral escape from immune response through engagement of KIRs (Heatley et al., 2013; Hölzemer et al., 2015). However, this viral evasion strategy needs to be investigated in more detail.

5.8 | Evasion of antibodies and the complement system

Viral interference with the complement system can be analyzed at several levels. First, some viruses can express viral proteins that mimic the cellular function of the cellular RCA (described in Section 2.4). HSV-1 encodes a C-glycoprotein which induces the dissociation of the altering C3 convertase pathway (Fries et al., 1986). Second, some enveloped viruses such as the Newcastle disease virus (Biswas et al., 2012) and vaccinia virus are able to incorporate host RCA (Vanderplassen et al., 1998) into its envelope by budding through the plasma membrane or intracellular vacuoles. Third, some viruses secrete a complement control protein (VCP) that shares similar amino acids with mammalian RCA and is able to interact with the proteins of the C3 convertase pathway (Agrawal et al., 2017).

Infected cells can also be lysed by complement-dependent antibodies. The binding of antibodies to epitopes on the surface of infected cells results in inactivation of the complement pathway and lysis of the cells. Some viruses produce molecules that bind to the Fc region of host immunoglobulins. Such virally encoded receptors (v-FcRs) may prevent IgGs from neutralizing free viruses (Daeron & Nimmerjahn, 2014; Lilley et al., 2001) and engaging antibody-dependent activity against the infected cells.

5.9 | Viral manipulation of host glucose metabolism

Recently, metabolomics has allowed a deeper understanding of host cell metabolic disorders induced by infectious diseases, which result from the infectious agent using the host cell's metabolism to their advantage for replication and persistence. Early studies have demonstrated the upregulation of glycolytic machinery during viral infection, which was seen from the replication of poliovirus in HeLa cells. Replication was blocked using a culture medium composed of solely a balanced saline solution, and next the proliferation and viral load were restored to their normal levels by restoring glucose supplementation (Darnell & Eagle, 1958). Subsequent studies have confirmed these findings, highlighting the molecular mechanism associated with glucose metabolism and the impact on the progression of HIV infection. After activation of T cells, a dramatic metabolic reconfiguration process occurs, which stimulates lymphocyte signaling to the detriment of the high bioenergetic demand influencing differentiation, growth, proliferation, and development of their effector functions (Buck et al., 2015).

It has been demonstrated that TCR activation and the costimulation of CD28 are required to allow maximal uptake of glucose by promoting upregulation and trafficking of glucose-cell transporter 1 (GLUT1) from the cell surface of T cells (Jacobs et al., 2008). In metabolically quiescent T cells, reverse transcription is blocked, as well as the integration of full-length HIV-1 DNA. Thus, the HIV genome remains mainly in the linear and nonintegrated form, mitigating viral replication (Bukrinsky et al., 1991; Chun et al., 1997). GLUT1 expression and glucose uptake appear to be essential for adequate CD4⁺ T-cell infection (Loisel-Meyer et al., 2012; Palmer et al., 2014). In the same way, Th17 responses are characterized by the expression of the C-C chemokine receptor 6 (CCR6) and hypoxia-induced factor 1 alpha (HIF-1 α), a central regulator of glucose metabolism (Shi et al., 2011).

It has been suggested that polarization towards the Th1/Th17 phenotype promotes HIV persistence during highly active anti-retroviral therapy (HAART), with Th17 being an important reservoir for HIV (Gosselin et al., 2017; Stieh et al., 2016). In accordance with this, evidence has shown that HIV-infected individuals treated with ART have decreased numbers of circulating CD4⁺ T cells expressing GLUT1 (Palmer et al., 2014), and this expression could be used as a measure of persistent immune activation associated with viral persistence.

Several other viruses also hijack the glycolytic machinery to their own advantage. KSHV induces aerobic glycolysis and lactic acid production, which decreases mitochondrial oxidative phosphorylation to maintain the latent state of the virus (Delgado et al., 2010). Hyperglycemic nude mice treated with telomerase-immortalized human umbilical vein endothelial KSHV-infected cells (TIVE-KSHV) have been shown to express higher levels of HSHV lytic genes (Ye et al., 2016). THP-1 cells infected by KSHV have shown hyperactivation of AKT and translocation of GLUT-1 to the plasma membrane of infected cells (Gonnella et al., 2013). Nontumorigenic breast epithelial cell line MCF10A infected by adenovirus activated MYC, a proto-oncogene, which increased glucose metabolism (Thai et al., 2014). DENV-infected cells have shown various glycolytic metabolites that are over-regulated in the early postinfection stage and downregulated in later stages (Fontaine et al., 2015).

Owing to interest in the recent outbreaks of fetal microcephaly induced by Zika virus infection, it was proposed that Zika modulates GLUT1 function by preventing normal glucose flow in placental endothelial cells, impacting normal fetal growth (Blonz, 2016). As with other viruses of the Flavivirus family, the Zika infection is similar to DENV. They use glucose uptake to increase bioenergetic demand and cellular biomass. Therefore, it is not surprising that viral modulation of glucose metabolism in the host cell is required for optimal virus replication (Jordan & Randall, 2016).

A perfect mechanism of viral evasion is confirmed by the virus-induced changes in host glycolytic machinery, which are essential for the development of a successful infection and are likely to contribute to the pathogenesis observed in distinct infections. Nevertheless, the precise molecular mechanisms that drive this reprogramming continue to be researched. In the future, pharmacological drugs that specifically target lymphocytes and the glycolytic pathway could be combined with antiviral therapies to achieve a better clinical outcome.

5.10 | Modifications of the redox environment and activation of virus-induced signaling pathways

Cell signaling pathways are activated or inhibited by modulation of the redox environment, resulting in the production of reactive oxygen and/or nitrogen species as the initial trigger during a viral infection. The virus-promoted redox changes can induce conformational changes in key host proteins, contributing to the success of their viral replication.

HIV infections are typically accompanied by chronic micro-inflammation and T-cell activation with high levels of inflammatory cytokine secretion, and high levels of intracellular generation of ROS (Emilie et al., 1994; Israël & Gougerot-Pocidallo, 1997). The underlying persistent oxidative stress results in an imbalance of the intracellular antioxidant defenses. Decreased glutathione (GSH) and thioredoxin (Trx) levels have been consistently reported during HIV-1 infection (Eck et al., 1989; Masutani et al., 1992; Nakamura et al., 1996; Peterhans, 1997; Staal et al., 1992). Thus, the use of

antioxidants to reduce ROS levels in HIV-infected patients has been extensively examined (Allard et al., 1998; R. Lee et al., 1997; Mandas et al., 2009; Martin et al., 2001).

The imbalance between ROS production and elimination during HIV-1 infection is well established (Kruman et al., 1998; Yang et al., 2009). Several groups have demonstrated these events either by measuring H₂O₂ production and the viral load or by comparing the regulation of transcription factors (e.g., NF- κ B) during the interplay between ROS production and HIV-1 replication (Mihm et al., 1991; Nabel & Baltimore, 1987). These results suggest that distinct pathways regulate ROS turnover with a direct impact on HIV-1 replication (Kruman et al., 1998; Schreck et al., 1991; Westendorp et al., 1995). In addition, the signaling free radical NO also plays an important, albeit dual role in HIV-1 infection. NO may be beneficial to the host through inhibition of viral enzymes or damaging (harmful) through activation of cellular signaling proteins that will support virus replication (Bogdan, 2001; Krogh et al., 2014; Mannick, 1995; Mannick et al., 1999).

As the protective and toxic effects of NO production often co-exist, different NO concentrations should also be correlated with pathological and cytotoxic states (Beckman & Koppenol, 1996). The pathogenic effects of NO-mediated events depend upon the formation of secondary intermediates, such as peroxyne nitrite anion (ONOO⁻) and nitrogen dioxide (NO₂), which are more reactive than NO itself (Brito et al., 1999; Radi et al., 2001). The interplay between ROS and NO is involved in normal and pathological conditions primarily through the nitration of tyrosine residues on target proteins (Bogdan, 2001).

A recent study analyzed human brains from individuals who had HIV infection without encephalitis and with encephalitis and compared both groups to the brains of healthy individuals. Nitrated proteins were predominantly found in HIV-infected individuals with encephalitis (Uzasci et al., 2014).

Cairolì et al. showed that peripheral blood mononuclear cells from HIV-infected patients showed a significant decrease in NO production and iNOS messenger RNA (mRNA) expression. A decrease in NO levels during infection may favor disease progression, possibly due to the loss of antiviral and antiapoptotic activities (Cairolì et al., 2008).

The cellular redox state in lymphocytes may be modulated by endogenous generation of ROS and NO. These reactive species can interfere with the biochemical parameters of cell activation (Lander, 1996; Lander et al., 1996). Furthermore, exogenously supplied oxidants such as haemin and the NO donors sodium nitroprusside (SNP) and S-nitroso-N-acetylpenicillamine (SNAP), stimulate tyrosine phosphorylation and regulate signaling pathways in fibroblasts, endothelial cells and lymphocytes (Curcio et al., 2010; Lander et al., 1993). However, the redox regulation of signaling pathways triggered by HIV infection is poorly understood.

Curcio et al. analyzed ROS/NO production and antioxidant cellular defenses in response to HIV-1 infection in CD4⁺ T cells obtained from healthy individuals, in the presence and absence of SNAP. Infected cells showed lower NO production and higher ROS and antioxidant enzyme levels compared to uninfected cells. Analysis

of the redox pair GSH/GSSG (reduced glutathione/glutathione disulfide) suggested the presence of an oxidizing intracellular redox environment in infected cells that was probably a consequence of virus infection. Additionally, the phosphorylation levels of PKC, Src kinase, and Akt in CD4⁺ T cells were modified after infection. In addition, after exposing infected cells to SNAP, we observed that ROS production and SOD1 activity were decreased if compared to infected cells without SNAP treatment. Importantly, exposure of HIV-infected CD4⁺ T cells to SNAP stimulated the PKC, Src kinase, and Akt signaling axis with major consequences for the viral load and viral integration.

6 | MECHANISMS OF SARS-COV-2 EVASION

6.1 | CpG deficiency

CpG deficiency is a common feature of ssRNA viruses, including coronaviruses (Atkinson et al., 2014; Greenbaum et al., 2008, 2009; Takata et al., 2017; Yap et al., 2003). The zinc-finger antiviral protein (ZAP) binds specifically to CpG dinucleotides in viral RNA genomes and is responsible for IFN-mediated immune response (Meagher et al., 2019). SARS-CoV-2 has the lowest index CpG (ICpG) when compared to their viral genome relatives (Xia, 2020). It has been suggested there is an association between decreased CpG and increased virulence in many publications related to diverse viral RNA genomes (Antzin-Anduetza et al., 2017; Burns et al., 2009; Fros et al., 2017; Theys et al., 2018; Trus et al., 2020; Tulloch et al., 2014; Wasson et al., 2017).

6.2 | 2'-O-methylation of viral RNA

Coronaviruses methylate their viral mRNA 5' cap structures through two self-made enzymes denominated N7-methyltransferase and 2'-O-methyltransferase (2'-O-MTase) (Bouvet et al., 2010; Chen et al., 2009). 2'-O-methylation of mRNA protects viral RNA from recognition by Mda5 (Züst et al., 2011) and IFIT (IFN-induced proteins with tetratricopeptide repeats) (237) family members and contributes to evasion of the IFN-mediated restriction of viral replication (Daffis et al., 2010; Züst et al., 2011). SARS-CoV-2 is a unique virus that requires interaction between the nsp10 and nsp16 proteins for nsp16 to execute its 2'O-MTase activity (Chen et al., 2011; Decroly et al., 2011; Encinar & Menendez, 2020; Lugari et al., 2010).

6.3 | Viral suppressor of RNAi (VSR)

The nucleocapsid protein (N protein) of SARS-CoV-2-infected human cells has shown suppression of antiviral RNAi activity (Mu et al., 2020). A previous study of N protein on SARS-CoV demonstrated a resembling effect, suggesting that N proteins function as a VSR (Cui et al., 2015). Similar VSR activity in coronavirus genome relatives

might be explained by the high homology (94%) among coronavirus N proteins (Mu et al., 2020).

6.4 | Orf8 protein

A phylogenetic analysis of the accessory protein orf8 from SARS-CoV and SARS-CoV-2 revealed that this new coronavirus has an orf8 distant from the conserved one derived from human SARS-CoV. This novel orf8 probably impairs the activation of intracellular stress pathways and of NLRP3 inflammasomes, due to the absence of an aggregation motif (VLVVL—amino acids 75–79) that is found on SARS-CoV orf8b that might initiate said activation (Chan et al., 2020). Orf8 might also down-regulate MHC class I molecules on the surface of various cell types, disrupting antigen presentation and reducing the recognition and elimination of virus-infected cells by CTLs (Park, 2020; Y. Zhang et al., 2020).

6.5 | Orf3b protein

The SARS-CoV-2 orf3b protein presents only 32% amino acid identity homology to SARS-CoV, indicating the codification of a novel orf3b short protein (Chan et al., 2020). A previous study has found that orf3b is capable of inhibiting the expression of IFN- β at synthesis and signaling levels (Kopecky-Bromberg et al., 2007). A recent study has shown that the orf3b of SARS-CoV-2 and SARS-CoV not only differ in their length but also in their ability to antagonize IFN type I (Konno et al., 2020). Surprisingly, ORF3b is highly detectable during the early phase of SARS-CoV-2 infection (Hachim et al., 2020) and impaired IFN type I responses as well as reduced IFN-stimulated gene expression are associated with severe COVID-19 disease in patients (Hadjadj et al., 2020).

7 | CONCLUSION

Viruses can use the host's machinery and develop mechanisms to mislead the immune system to ensure their replication and spread through organisms. This review discusses some of these mechanisms and highlights the importance of understanding them to support the development of novel pharmacological strategies to treat viral infections.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable, no new data generated. Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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