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Review article

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Human herpesvirus evasion of humoral immunity and implications for vaccine development

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Abstract

Herpesviruses are highly species-specific, having co-evolved with their respective hosts over millennia. This evolutionary relationship has led to the development of highly specialized immune evasion strategies, enabling these viruses to establish lifelong infections. Periods of immunosuppression can lead to severe disease, such as graft rejection, cancer, neurodegenerative disease and autoimmune diseases, which have been linked to herpesvirus infections. Consequently, developing strategies to prevent herpesvirus-associated diseases is a critical public health priority. However, varicella zoster virus (VZV) remains the only human herpesvirus for which licensed vaccines are available. This Review explores the mechanisms of humoral immune evasion by herpesviruses and their implications for advancing immunization and treatment strategies for chronic neurological, oncological and transplant-associated diseases caused by these common viral pathogens.

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Introduction

There are nine herpesviruses known to infect humans, which are divided into three subfamilies. Herpes simplex virus 1 (HSV-1), HSV-2 and varicella zoster virus (VZV) are alphaherpesviruses; cytomegalovirus (CMV), human herpesvirus 6A (HHV-6A), HHV-6B and HHV-7 are betaherpesviruses; and Epstein–Barr virus (EBV) and Kaposi sarcoma-associated herpesvirus (KSHV) are gammaherpesviruses. They represent a unique challenge in preventive medicine due to their high seroprevalence in the human population and their ability to evade nearly every attempt at elimination by the host immune system, including innate, adaptive and even intracellular immunity to establish latency[1–7]. Following infection, herpesviruses remain in the body for life, where they persist subclinically but can reactivate symptomatically during periods of immunosuppression[1,8]. Acute infections with these viruses are typically only mildly symptomatic in healthy adults but can cause severe disease in newborns infected in utero or very early in life as well as in adults during periods of immunosuppression. Alphaherpesviruses and betaherpesviruses can cause severe acute disease in young children and have been associated with neurodegenerative diseases, whereas gammaherpesviruses are frequently associated with malignancies or autoimmunity[1,8–13]. Consequently, strategies to prevent these disease outcomes are paramount to long-term human health. Despite this need, VZV remains the only human herpesvirus for which vaccines are licensed for clinical use to prevent severe acute disease (varicella; also known as chickenpox) and its reactivation-associated disease, called herpes zoster (shingles)[14–20].

There are two major approaches to herpesvirus vaccination, and vaccines against VZV provide the only licensed examples of both. The first is prophylactic vaccination, administered prior to infection to prevent infection or ameliorate disease from acute infection. In the case of VZV, two live-attenuated virus vaccines and a combined measles–mumps–rubella–varicella vaccine are administered to children for prevention of varicella, and these vaccines have been extremely efficacious in reducing the incidence of disease, hospitalizations and mortality[21,22]. Although it is important to note that replication-competent herpesvirus vaccines, even though attenuated, will establish latency in the immunized individual and can reactivate and cause disease, studies of the VZV vaccines found that herpes zoster occurred less frequently in vaccinees compared with individuals infected with wild-type VZV[23,24]. The second approach is therapeutic vaccination, often associated with chronic diseases such as cancer and autoimmunity. Therapeutic vaccines are administered after initial infection and are intended to prevent disease associated with viral reactivation or secondary infections[25]. Shingrix (GlaxoSmithKline) is the primary vaccine recommended for prevention of shingles; it is composed of recombinant glycoprotein E (gE) adjuvanted with AS01B[26,27] and demonstrates 97% efficacy in preventing shingles[28,29]. Although VZV vaccines have been very effective, the immune responses associated with protection have not been well defined, even though efficacy is often attributed to cellular immunity rather than antibody-mediated immunity[30].

Substantial efforts have been made to license vaccines for other herpesviruses, including human CMV (HCMV), EBV and HSV. Multiple HCMV vaccines have been tested in phase II clinical trials, including an adjuvanted protein subunit vaccine containing the primary fusogen (glycoprotein B (gB)) of the virus, a replication-defective whole virus vaccine, and an mRNA vaccine containing gB and the five components of the pentameric complex[31]. Only Moderna's mRNA-1647 has advanced to phase III trial[32], but failed to meet the required efficacy end point for prevention of HCMV acquisition in women who were HCMV-negative; however, this vaccine is also currently being evaluated in phase II for another key target population of recipients of allogenic haematopoietic cell transplant[33–35]. Moderna also has two ongoing phase I/II trials for EBV vaccines: mRNA-1189 containing gp42, gp220, glycoprotein H (gH) and glycoprotein L (gL) for prevention of EBV infection and mononucleosis[36]; and a proprietary formulation (mRNA-1195) for therapeutic use in individuals with multiple sclerosis[37]. EBV vaccines to date have largely focused on eliciting neutralizing antibodies against the major glycoprotein gp350, including a current nanoparticle vaccine in a phase I trial[38], but promising recent preclinical studies have aimed to elicit broad immune responses involving both B cell and T cell arms of adaptive immunity[39]. HSV vaccine development has been of interest to many pharmaceutical companies for both prophylactic and therapeutic purposes, with several protein subunit vaccine candidates completing phase III trials but none advancing to licensure[40]. Other vaccine platforms have been applied to HSV in the past decade, including multiple trials of mRNA-based vaccines, yet none has advanced to phase III trial[40].

Vaccine development for the prevention of herpesvirus-induced diseases faces several key challenges, which have contributed to the relatively small number of clinically approved vaccine products. Perhaps the biggest limitation is that herpesviruses are highly species-specific, and therefore animal models for assessing vaccine efficacy are limited and much less translatable than models for less species-specific pathogens[41–45]. Furthermore, studying the basic biology of these viruses is primarily done in vitro due to animal model limitations. Researchers have largely utilized observational clinical studies to learn about human herpesviruses or studied an animal model specific virus in vivo, both of which are approaches that come with significant limitations. However, we understand that the relationship between these viruses and the host immune system is incredibly complex as all herpesviruses utilize numerous immune evasion mechanisms against innate and adaptive immune responses[46–49]. In this Review, we describe immune evasion mechanisms that allow herpesviruses to subvert humoral immunity, a key component of vaccine-elicited immunity (Fig. 1). We further explore the implications of these mechanisms on the development of herpesvirus immunization strategies and outline the resulting areas of research.

The role of antibodies in herpesvirus control

The prototypical role of antiviral antibodies is neutralization, in which the antigen-binding fragment (Fab) region of the antibody binds to its specific antigen on the virus and prevents the virus from infecting host cells. For vaccine development, neutralizing antibodies are frequently key to achieving the high level of sterilizing immunity, wherein pre-existing immunity prevents infection of a naive host. Achieving this generally requires sufficient amounts of neutralizing antibodies to be present at potential sites of infection when exposure to the pathogen occurs[50]. Herpesviruses are most often spread through contact with infected bodily fluids at mucosal sites[51–53], where the antibody landscape differs substantially from that of plasma, with IgA often dominating over IgG[54]. However, the importance of mucosal IgA in prevention of herpesvirus infections has not been studied thoroughly, and vaccine studies rarely look beyond plasma IgG responses. Furthermore, existing immunity, including naturally induced neutralizing antibody responses, is often not protective against reinfection with another strain of the same virus[55,56], potentially reflecting the limited potency of naturally elicited neutralizing antibodies against herpesviruses.

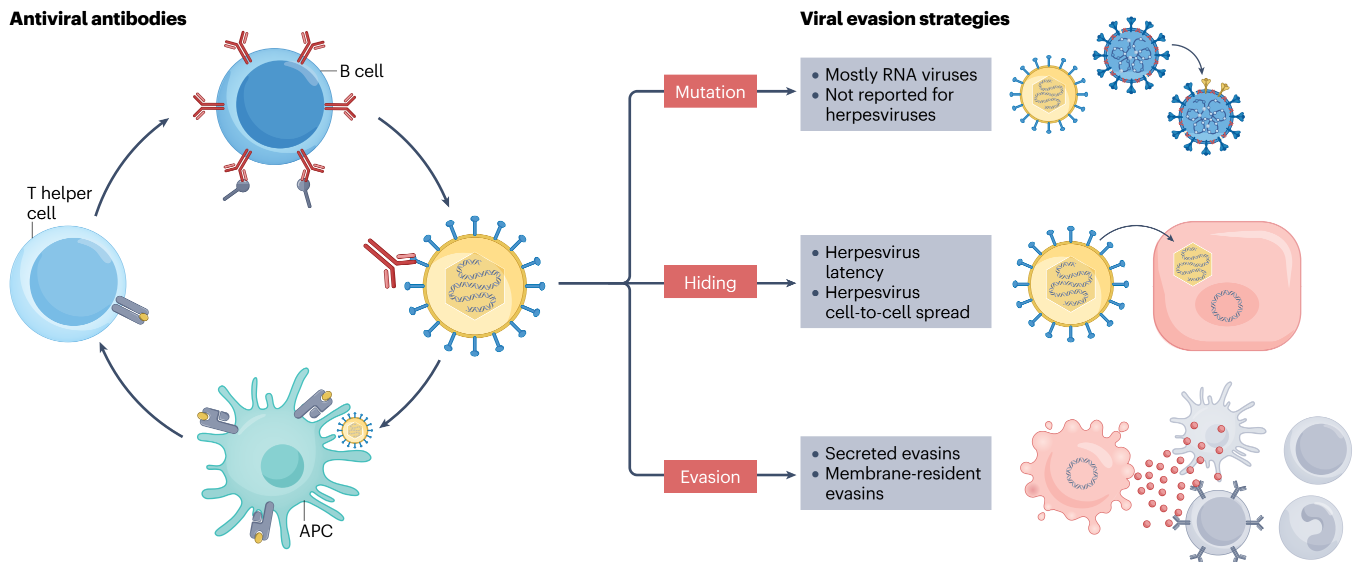


Fig. 1 | Overview of herpesvirus strategies to evade host humoral immunity. The immune system is adept at addressing foreign particles in the body through innate immune sensing and adaptive immune memory. Viruses evade the immune system through mechanisms that can be summarized in three categories: change via mutations or dominance of variants that provide a fitness advantage; hide inside cells and disseminate through cell-to-cell spread; and evade immune detection and clearance through expression of a myriad of viral proteins that directly interact with the immune system to prevent detection and clearance of the virus. Herpesviruses have utilized multiple strategies to establish a balance with their respective host immune responses that allows latency; as large DNA viruses, however, herpesviruses are slow to adapt via mutations but utilize numerous mechanisms to hide and evade host immunity.

Beyond neutralization, some antibodies, particularly IgG, can also serve as immune sentinels to mediate other antiviral effector functions through interactions involving the crystallizable fragment (Fc) distal from the Fab–antigen binding interaction. The Fc portion of virus-specific IgG can interact with complement component C1q to initiate the complement cascade[57], or with Fcγ receptors (FcγRs) to initiate cellular effector functions such as antibody-mediated cellular phagocytosis and antibody-mediated cellular cytotoxicity (ADCC)[58,59]. Similar to T cell responses, Fc-mediated effector functions typically act on infected cells and thus likely serve to limit dissemination, help to clear viral infection and prevent reactivation but act too late to play a role in preventing infection[58,59]. Despite this delayed impact, a growing body of evidence implicates herpesvirus-specific Fc-mediated effector functions in protection from key disease outcomes, including but not limited to neonatal HSV infection, congenital HCMV infection and development of EBV-associated nasopharyngeal carcinoma[60–64]. A summary of how antibodies may play a role in limiting herpesvirus-associated disease is shown in Table 1.

Studies of mouse CMV (MCMV) have demonstrated that although antibodies are not essential for control of primary infection — as B cell-deficient mice are able to clear MCMV as efficiently as their immunocompetent counterparts — antibodies play a pivotal role in limiting dissemination following reactivation of latent virus and reinfection with a new strain[65–68]. Thus, although many elements of immunity will likely be important considerations for development of disease prevention strategies, antibody-based interventions carry immense potential for clinical impact in reduction of disease burden. Antibodies are a key component of vaccine-elicited responses, but they may also be utilized for passive immunization. For example, prophylactic treatment with a potently neutralizing rhesus CMV (rhCMV) hyperimmune globulin (HIG) demonstrated the ability to protect against placental transmission after primary maternal infection during pregnancy even in the high-risk setting of $CD4^+$ T cell depletion, which otherwise results in 100% fetal infection[69]. This contradicts the human clinical trial assessing an HCMV HIG therapy for prevention of vertical CMV transmission following a primary maternal infection, which was stopped early for futility[70]. The discrepancy in these results may be explained by the timing of administration, which was before challenge in the non-human primate experiment and after infection was diagnosed in the clinical trial[69,70]. Similarly, a trial assessing the incidence of EBV-associated post-transplant lymphoproliferative disorder after antiviral medication with and without infusion of IgG from healthy people found no effect of the IgG treatment[71]; however, the IgG product used was not enriched for EBV antibodies, and a follow-up experiment utilizing a humanized mouse model found that EBV HIG treatment reduced the plasma viral load significantly compared with saline-infused controls and also showed a modest reduction compared with non-EBV-enriched IgG[72]. Passive immunization has largely been studied in the context of preventing infection with a focus on neutralizing antibodies, but given the importance of Fc effector functions in preventing disease outcomes, antibody therapies may be useful in reinfection-associated disease as well. Furthermore, passive immunization strategies may be especially useful in vulnerable, immune-suppressed individuals whose immune systems may not respond fully to active vaccination. However, it has been noted that memory B cell responses to HCMV can occur independently of T cell help in mice[73], suggesting that T cell-targeted immunosuppression may not dampen humoral responses, thereby keeping active vaccination strategies a viable option for these high-risk populations.

The likely importance of antibody functions is further underscored by the efforts herpesviruses make to elude them, which we explore in the following section.

Humoral immune evasion mechanisms of herpesviruses

Cell-to-cell spread

One mechanism through which herpesviruses can evade humoral immunity is a preference for cell-to-cell spread over free virus-dependent dissemination, making them less susceptible to neutralizing antibodies[74] (Fig. 2). There are several mechanisms of cell-to-cell spread, but syncytia formation and spread at cell junctions are the primary mechanisms utilized by herpesviruses. Herpesviruses enter host cells through membrane fusion of the viral envelope and cell membrane through highly conserved mechanisms mediated by gB and the gH–gL complex, and these proteins are additionally important for cell-to-cell

Table 1 | Potential role of antibodies in herpesvirus disease prevention

Pathology	Herpesvirus	Associated disease	Potential role of antibodies in prevention[a]	Potential key antibody functions
Acquisition	All	NA	Sterilizing immunity likely unachievable[55,56,180]	Neutralization
Acute disease	HSV	Herpes (skin lesions)	Control active infection quickly and prevent severe disease, in combination with T cell responses[20,65,180]	Role for neutralization but Fc effector functions likely more important[199,200]
	VZV	Varicella (also known as chickenpox)		
	EBV	Mononucleosis		
	CMV			
	HHV-6B	Roseola		
	HHV-7			
Establishment of latency	All	NA	Prevention of dissemination to sites or cell types that support latency[67]	Cell-to-cell spread inhibition, Fc effector functions
Reactivation	VZV	Shingles	Control reactivated virus quickly and limit spread[68]	Cell-to-cell spread inhibition, Fc effector functions, possibly some neutralization
	HSV-1	Oral cold sores		
	HSV-1, HSV-2	Genital herpes		
Reactivation in immunocompromised individuals	Multiple	Pneumonia		
		Encephalitis		
		Hepatitis		
Reinfection with the same virus strain	All	NA	Memory response sufficiently protective[67]	Neutralization
Reinfection with a different virus strain	All	NA	Incomplete memory response due to new or different antigens, only partially protective[201]	Neutralization[202]
Horizontal transmission	All	NA	Reduce amount of viral shedding in bodily fluids	Conflicting evidence, potential role for many antibody functions and T cell responses[203,204]
Vertical transmission	HCMV	Congenital and perinatal CMV[197]	Limit transmissible virus at maternal–fetal interface and in birth canal[63]	Fc effector functions[61,62,64]
	HSV	Neonatal HSV		
Transplant complications	HCMV	Organ damage, rejection, graft-versus-host disease[205,206]	Limit viral reactivation by targeting infected cells	Inhibition of cell-to-cell spread, Fc effector functions[176,183,207,208]
	EBV	Post-transplant lymphoproliferative disorder[209]		
	HHV-6B	Central nervous system infections after stem cell transplant[210,211]		
Malignancies	EBV	Lymphomas, nasopharyngeal carcinoma, etc.	Control of latently infected cells[212,213]	Fc effector functions
	KSHV	Kaposi sarcoma, primary effusion lymphoma		
Autoimmunity	EBV	Multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis[214]	Control of latently infected cells, limit reactivation and chronic antigen exposure[214,215]	Fc effector functions
	HHV-6	Hashimoto's thyroiditis, systemic lupus erythematosus, rheumatoid arthritis[215]		

CMV, cytomegalovirus; EBV, Epstein–Barr virus; Fc, crystallizable fragment; HCMV, human CMV; HHV, human herpesvirus; HSV, herpes simplex virus; KSHV, Kaposi sarcoma-associated herpesvirus; NA, not applicable; VZV, varicella zoster virus. [a]In some cases, certain types of antibodies may play a detrimental role.

spread as membrane fusion between infected and uninfected cells is a critical step[75,76]. VZV and HSV-2 more commonly use syncytia formation, resulting in dissemination and pathology in the form of skin lesions[76,77]. For other herpesviruses, membrane fusion during cell-to-cell spread is less common with syncytia formation occurring when components of their typical cell-to-cell spread machinery are dysregulated[78,79], and cell fusion is more commonly observed in vitro with culture-adapted virus strains[80]. HCMV, for example, demonstrates limited points of membrane fusion[81]. Although key components of membrane fusion are conserved among herpesviruses, there are also virus-specific cell-to-cell spread mechanisms that utilize unique glycoproteins that are likely to play a role in cell tropism. For example, HSV glycoprotein D (gD; encoded by *US6*) participates in cell–cell fusion along with gB and gH–gL, but syncytia formation is regulated by glycoprotein K (gK)[82,83].

Although cell-to-cell spread enables viruses to evade prototypical neutralizing antibodies, some antibodies can inhibit cell-to-cell spread, and these antibodies have been associated with protection against viral reactivation in a study of individuals infected with HSV-1 and protection from genital herpes in a guinea pig model[84,85]. However, the accessibility of target epitopes that mediate cell-to-cell spread is greatly reduced, and eliciting cell-to-cell spread inhibitory antibodies may not be simple[86,87]. In the case of HCMV, a study examining sera from elite neutralizers for their ability to limit cell-to-cell spread found that inhibition of cell-to-cell spread was very rare[88]. This inability of anti-HCMV antibody to block cell-to-cell spread could be one aspect to the repeated ineffectiveness of HIG treatment to block or ameliorate congenital HCMV infection following acute HCMV infection in pregnancy in clinical trials, and why only partial success was achieved with very high HIG dosage and very early onset of treatment post exposure[70,89,90]. It is possible that enriching for neutralizing antibodies reduces other antibody functions, including a capacity for inhibiting cell-to-cell spread. Similarly, the only partial success of HCMV and HSV vaccines that mainly targeted neutralizing antibodies could also be explained by the highly cell-associated nature of these viruses. The induction of potent virus-neutralizing antibody responses is widely considered to be a gold standard of antiviral vaccine strategies. Yet antibodies with more complex antiviral activities, such as reducing cell-to-cell spread or clearing infected cells via Fcγ-mediated immunity, may be required for protection against disease in the case of the highly cell-associated herpesviruses.

Involvement of multiple viral glycoproteins and host receptors in pathogenesis

As large, enveloped DNA viruses, the herpesvirus family encodes multiple surface glycoproteins that play important roles in the viral life cycle and pathogenesis (Fig. 3). Unlike other virus families, which often use a single surface glycoprotein that mediates both receptor binding and viral membrane fusion, herpesviruses divide these functions among multiple glycoproteins[75]. gB, gH and gL are some of the most conserved glycoproteins between the human herpesviruses and all play indispensable roles in viral entry[75]. However, each herpesvirus can infect multiple cell types and utilizes different glycoproteins to interact with different host proteins as entry receptors mediating broad tropism[75]. As entry mechanisms are split across different viral antigens, the immune system, in theory, must target multiple glycoproteins to effectively

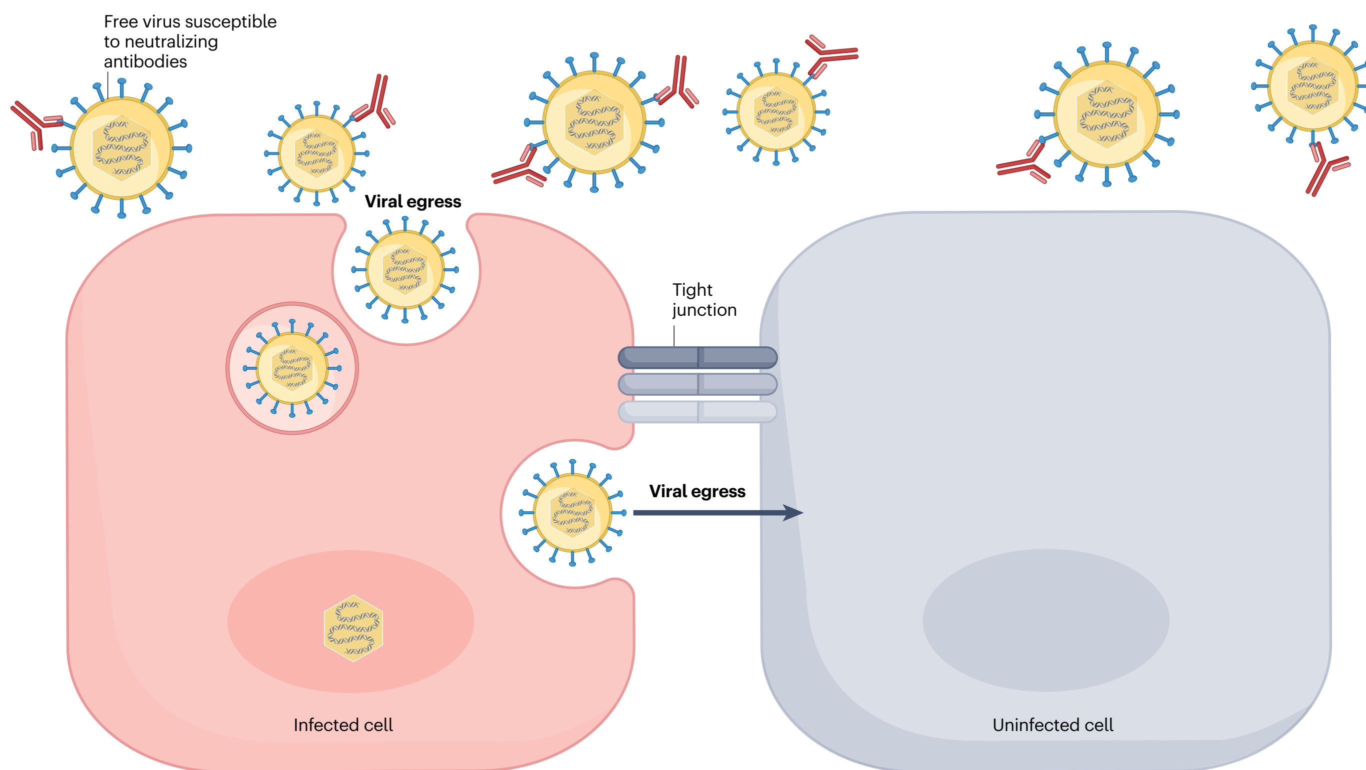
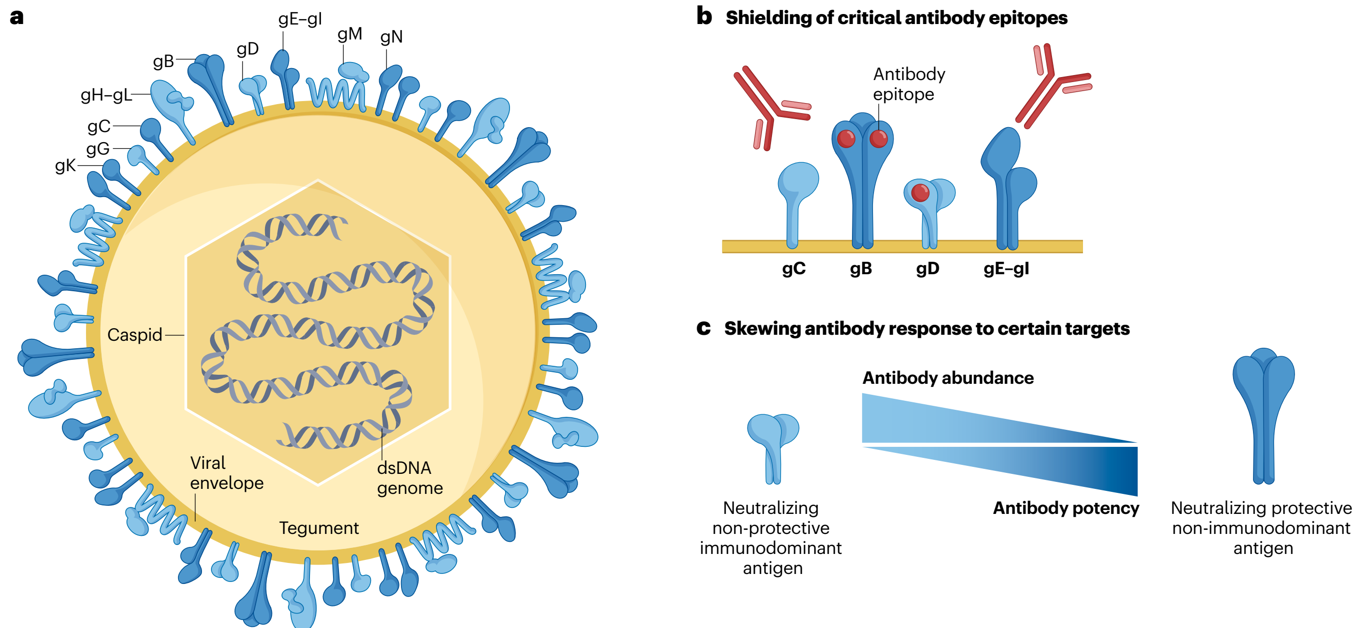
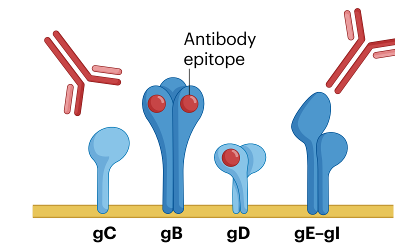


Fig. 2 | Herpesviruses can evade humoral immunity through cell-to-cell spread. Virus egress from infected cells into extracellular space can be readily detected by the immune system and targeted by neutralizing antibodies. Cell-to-cell spread through syncytia formation or spread across tight junctions are mechanisms of herpesvirus dissemination that are less susceptible to antibody-mediated immunity with limited accessibility of antigens mediating cell-to-cell spread.





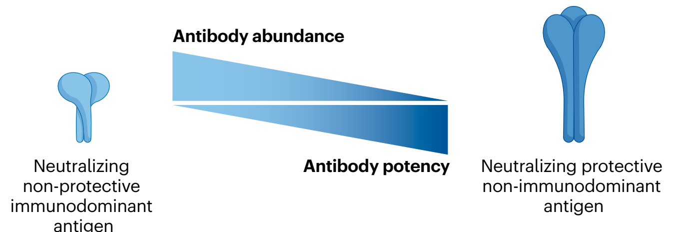


Fig. 3 | Glycoprotein diversity and potential mechanisms of humoral immune evasion. a, Cross-section of a herpes simplex virus (HSV) virion as an example, with labelled sections of the virus. A portion of the known named envelope glycoproteins are displayed. **b**, Models of glycoproteins blocking access to neutralizing antibody epitopes. Glycoprotein D (gD) and glycoprotein B (gB) are sites of dominant antibody responses and antibodies targeting these proteins are frequently neutralizing. The presence of glycoproteins such as glycoprotein C (gC) or glycoprotein E (gE)–glycoprotein I (gI) on the surface of the virus could occlude critical epitopes through steric hindrance of antibody binding, thus protecting the virus from neutralization. **c**, HSV splits entry mechanisms between different glycoproteins. gD mediates host cell receptor binding, subsequently triggering membrane fusion via gB. Both glycoproteins are immunogenic, but emerging evidence suggests that, in mice, gD may be immunodominant to the advantage of the virus, where antibodies targeting gB that mediate effector functions such as antibody-mediated cellular cytotoxicity (ADCC) are more protective than neutralizing antibodies that target gD, which may partially explain gD-specific vaccine failures in humans. dsDNA, double-stranded DNA.

mount a protective immune response. This diversity of entry pathways may benefit the virus as a division of resources by the host immune system and immunodominance of certain viral antigens may lead to a skewed immune response and poor protection[91]. For instance, the majority of IgG elicited against EBV targets gp350 (encoded by *BLLF1*), and gp350-specific antibodies can prevent EBV infection of B cells but do not contribute to neutralization on epithelial cells[92]. Another example is gD for HSV-1 and HSV-2, which mediates receptor binding and initiates viral entry[93]. In humans, this antigen is immunodominant[94] and has been used in multiple vaccine trials, all of which have failed to reach their end-point goals[95]. However, research groups have observed that a disabled infectious single-cycle HSV vaccine candidate lacking gD (ΔgD) resulted in a more protective immune response than the response produced by a gD-2 subunit or an alternative replication-deficient vaccine[96,97]. It is possible that through the deletion of gD, the absence of the glycoprotein on the virion surface opens access to previously occluded epitopes on other viral antigens that could result in a more protective immune response. Another possibility includes the shifting of the immunodominant antibody response that is usually elicited towards gD to gB instead[94]. gB, as the viral fusion protein, is a crucial target for the immune system as this glycoprotein mediates fusion with host cell membranes. Blocking this step either through direct neutralization of gB activity or by blocking interaction of gB with gH–gL is a mechanism by which gB-specific antibodies can neutralize HSV, limiting the establishment of infection. The ΔgD vaccine candidate elicits a gB-specific antibody response in mice and elicits antibodies that more robustly mediate effector functions than gD-specific vaccine-derived antibodies[96,98].

Beyond serving as a potential distraction for the immune response, glycoproteins on the virion surface can shield other glycoproteins from antibody recognition. It has been observed that for HSV-1, the presence of glycoprotein C (gC; encoded by *UL44*) on the envelope can shield epitopes on gB from neutralizing antibodies[99]. A panel of monoclonal antibodies targeting gB on HSV-1 were more potent against a ΔgC virus than against a wild-type virus, indicating that gC may prevent neutralization by blocking recognition of gB[99]. This finding extended beyond gB, as antibodies targeting gD and gH were more potent against ΔgC viruses as well[99]. The number of proteins on the surface of the virion may inhibit recognition by antibodies as these large proteins may physically hinder the ability of antibodies to bind, thus indirectly evading the immune response. Although the exact mechanism by which gC can potentially interact with and block recognition of other viral antigens remains to be determined, similar findings have been observed in other herpesvirus subfamilies, as the deletion of gp180 (encoded by *Bo10*) on bovine herpesvirus 4 (BoHV-4), a gammaherpesvirus, sensitized the virus to neutralization by immune sera by providing greater access to gB, gH and gL[100].

Additionally, some glycoproteins demonstrate variety among virus strains, which supports the potential for superinfection by strains expressing glycoproteins that differ sufficiently from those seen during initial infection. For example, five distinct genotypes of HCMV gB have been described[101], as well as eight genotypes of HCMV glycoprotein O

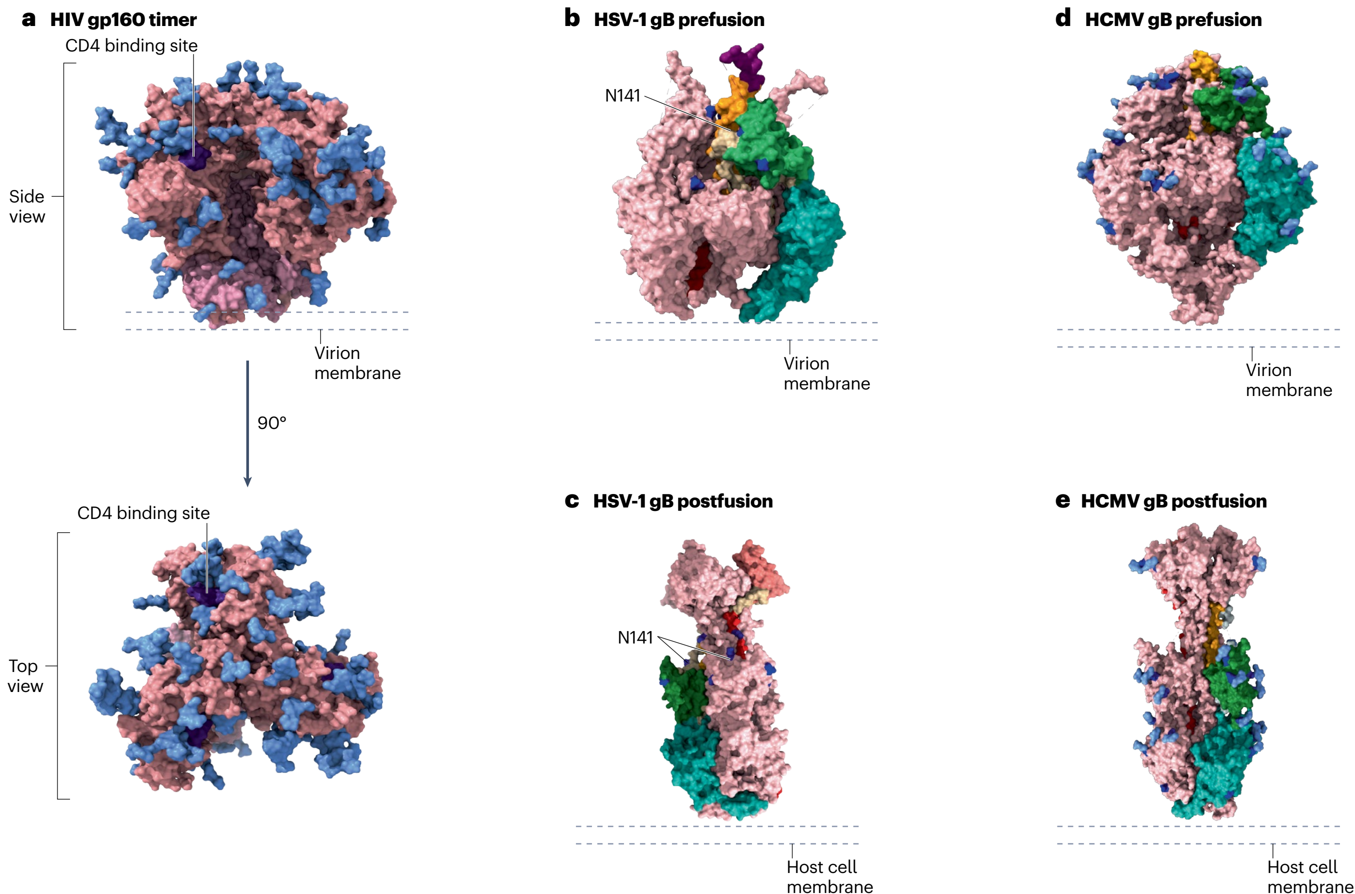


Fig. 4 | N-Linked glycan shielding of viral envelope glycoproteins. **a**, Prototypical example of a glycan shield represented on the surface of HIV-1 gp160 trimer (Protein Data Bank (PDB) ID 5ACO). Space-filling sugar moieties resolved in the structure are highlighted (light blue). The CD4 binding site is labelled (purple). Glycan structures decorate the surface of the protein, masking important neutralizing antibody binding regions. Resolved sugars in the structure may under-represent the glycan shield. **b**, Space-filling prefusion structure of herpes simplex virus 1 (HSV-1) glycoprotein B (gB) (PDB ID 6Z9M). Domains I–V of gB are coloured according to the scheme developed by Vollmer[216]. Possible N-linked glycan sites are highlighted (dark blue). N141 is labelled. **c**, Postfusion structure of HSV-1 gB (PDB ID 2GUM). Protein domains match the colours in panel **b**. Resolved possible N-linked glycan sites are highlighted (dark blue). N141 is labelled. **d**, Prefusion structure of human cytomegalovirus (HCMV) gB (PDB ID 7KDP). Domains I–V of HCMV gB are colour matched to HSV-1 gB domains. Resolved sugars in the structure are labelled (light blue). Resolved possible N-linked glycan asparagine residues are highlighted (dark blue). **e**, Postfusion structure of HCMV gB (PDB ID 7KDD). Domains I–V of HCMV gB are colour matched to HSV-1 gB domains. Resolved sugars in the structure are labelled (light blue). Resolved possible N-linked glycan asparagine residues are highlighted (dark blue).

(gO) that affect viral dissemination and susceptibility of the gH–gL–gO trimer to gH-specific neutralizing antibodies[102]. Taken together, these observations on the presence and diversity of glycoproteins on the surface of the virion indicate roles for these proteins in humoral immune evasion.

Glycan shielding

As envelope glycoproteins are also heavily glycosylated, the presence of sugar moieties may act as a glycan shield, hindering the humoral immune response (Fig. 4). Heavily glycosylated viral antigens may prevent antibody recognition in two ways: sugar residues are inherently poorly immunogenic, as their repetitive carbohydrate structures and similarity to self-glycans frequently result in a CD4$^+$ T cell-independent immune response[103,104]; and the large sugar moieties shield epitopes on the antigen from neutralizing antibodies reaching vulnerable epitopes[105,106].

For HSV-1, the absence of an N-linked glycan at position 141 on gB (encoded by *UL27*) resulted in greater antibody recognition, greater neutralization potency and greater ADCC responses, indicating that the glycan present as this residue acts as a shield preventing IgG from binding[107]. Recent evidence has demonstrated that several of the domains of HSV-1 gB that refold during fusion are occluded and masked by the presence of N-linked glycans[108]. These findings suggest that glycan shielding of the HSV-1 gB trimer is more extensive than previously appreciated and may impact neutralizing antibody responses. In the same study that reported that gp180 deletion increased the susceptibility of BoHV-4 to antibody neutralization, the authors observed that O-linked glycosylation of gp180 also acted as a glycan shield. The heavily glycosylated gp180 acted to shield both itself and neighbouring proteins from recognition by neutralizing antibodies[100]. Unlike viruses such as HIV or influenza virus, for which our understanding of how evolution within and between

hosts results in novel glycosylation sites that block access to epitopes is quite advanced[105,109], the evolution of a glycan shield for herpesviruses is incompletely understood. Envelope glycoproteins such as HSV gD and gB are required for entry, are frequent targets of neutralizing antibody responses and are heavily glycosylated. Given our knowledge of how glycan shields impact humoral immune evasion for HIV and influenza virus, as well as recent evidence demonstrating differential recognition of glycan mutants of the HCMV gB (encoded by *UL55*) AD-2 by monoclonal antibodies[110], we can hypothesize that these glycans may play a role in antibody evasion by herpesviruses. Many of the glycoproteins on HCMV are also extensively glycosylated[111], with the glycan shield of gB and glycoprotein N (gN) playing roles in immune evasion and resistance to neutralizing antibodies[112,113]. N-Linked glycosylation of HCMV gN directly contributes to humoral immune evasion as recombinant viruses with truncated gN were more susceptible to antibodies targeting gN as well as antibodies targeting gB and gH[112]. Similar evidence exists for HSV-1 gC, which is also highly glycosylated, as the presence of gC and its glycans may shield neighbouring glycoproteins such as gB and gD from neutralizing antibodies[99,114]. These glycosylation sites are important for viral protein stability[115] and viral pathogenesis[107]. More work using recombinant viruses is needed to investigate the potential effects of glycan shielding on important antibody epitopes by herpesviruses.

Viral cytokines and decoy receptors

Another way that betaherpesviruses and gammaherpesviruses modulate the host immune system is through expression of decoy cytokines and receptors[116,117]. These decoys modulate the innate immune response and inhibit inflammatory T cell responses, but due to the broad immunological effects of cytokines, some likely also impact the humoral response indirectly. HCMV encodes two IL-10 homologues expressed by splice variants of *UL111A*, one of which is associated with latent infection (LAcmvIL-10) and the other with lytic infection (cmvIL-10)[118–120]. Similar to human IL-10, the impact of viral IL-10 is largely immunosuppressive through downregulation of inflammatory cytokine production and MHC expression, and notable impacts on dendritic cell maturation that may affect the humoral response indirectly through modulation of antigen presentation and germinal centre activity[118,121–123]. Additionally, cmvIL-10 has a direct effect on the humoral response through Stat3 activation and B cell proliferation, which has been posited as a mechanism of shifting the overall immune response away from cellular antiviral responses, which are thought to be more effective in controlling HCMV infection than the humoral response[120] (Fig. 5). EBV also encodes an IL-10 homologue, BCRF1, that shares many of the same functions as cmvIL-10 (ref. 124). Although without a known IL-10 homologue, KSHV encodes an IL-6 homologue, which has demonstrated a role in B cell proliferation, and multiple macrophage inflammatory protein (MIP)-like proteins[117,125].

Betaherpesviruses and gammaherpesviruses are also known to encode various cytokine receptor homologues and cytokine-binding proteins, which can be membrane-associated signalling molecules or solubilized to sequester their respective binding partners[49,116,126,127]. Similar to the cytokine homologues, these proteins are known to shift

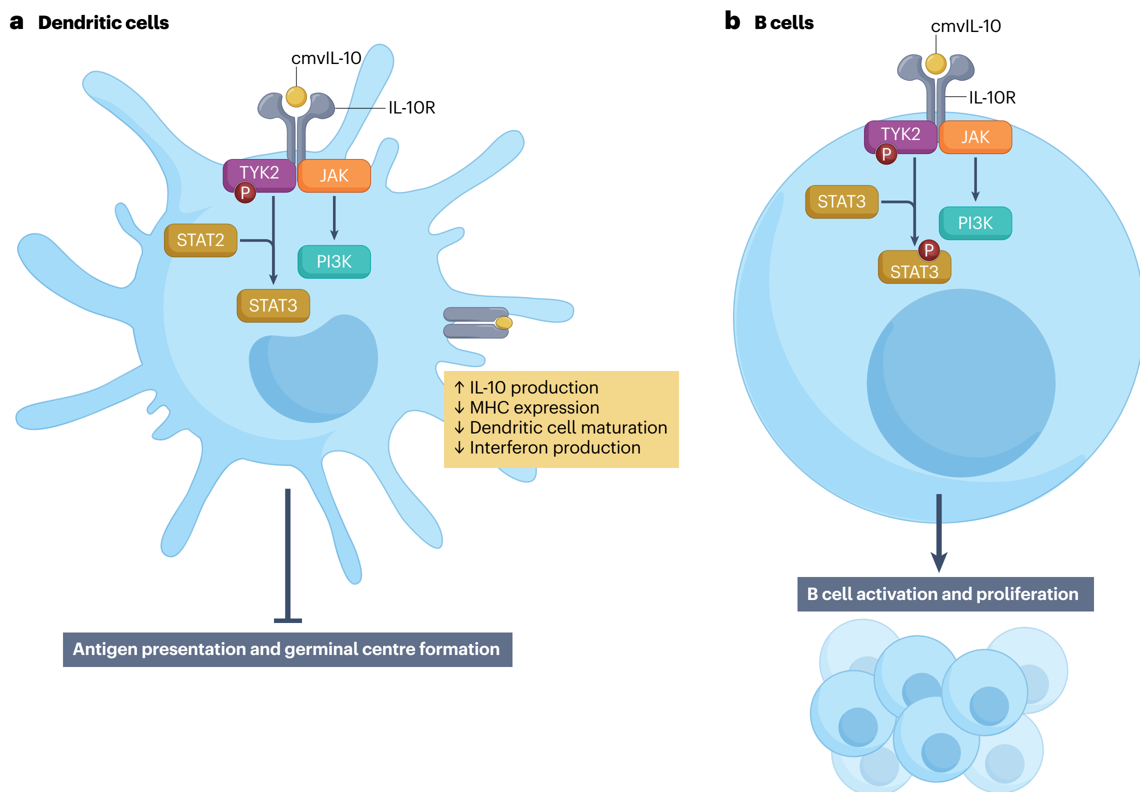


Fig. 5 | Viral cytokines suppress and skew the host immune response to infection. a, During infection, human cytomegalovirus (HCMV) expresses an IL-10 homologue (cmvIL-10) that can bind to host cell IL-10 receptor (IL-10R) on cells such as dendritic cells and acts as an immunosuppressive cytokine, dampening the host cell response to infection. **b**, cmvIL-10 is also thought to activate B cells and skew the immune response away from a T cell-mediated response towards a humoral response, which may be to the advantage of the virus.

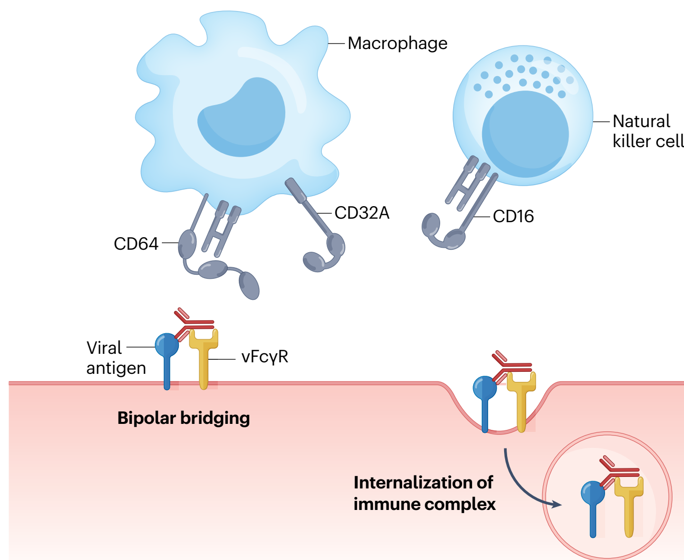


Fig. 6 | Viral Fc-binding proteins directly inhibit Fc effector functions. Human cytomegalovirus (HCMV), varicella zoster virus (VZV) and herpes simplex virus (HSV) encode membrane-associated proteins that bind to the crystallizable fragment (Fc) region of IgG called viral Fcγ receptors (vFcγRs). These proteins support viral immune evasion through multiple reported mechanisms. Antibody bipolar bridging (ABB) occurs when the antigen-binding fragment (Fab) region of the antibody binds to its target antigen, and vFcγRs in close proximity bind to the Fc region of the antibody. Bipolar bridging alone can be sufficient to prevent interaction with Fc receptors on host effector cells, such as macrophages or natural killer cells. However, these proteins have also been implicated in internalization and degradation or recycling of IgG captured in these immune complexes.

the immune response away from a T helper 1 (T_H1) cell response and towards a less traditionally effective T_H2 cell response[118]. For example, HCMV *UL21.5* encodes a decoy receptor specific for RANTES, a cytokine with broad functionality, including promotion of T_H1 cell differentiation[128]. The mRNA transcript for this receptor is packaged into virions, suggesting a role for this decoy RANTES receptor very early on in infection, even prior to viral transcription[129]. Notably, there are several membrane-associated G protein-coupled receptor homologues expressed by HCMV (US27, US28, US33 and UL78), HHV-6 and HHV-7 (U12 and U51), EBV (BILF-1) and KSHV (ORF74), which perform broad immunomodulatory functions[126,127,130–132]. For example, HCMV US28 has multiple ligands (RANTES, MCP1, MCP3, MIP1α and fractalkine), with significant functional consequences, including constitutive cellular activation supporting HCMV replication, increased motility of infected cells likely supporting viral dissemination, and a potential role in immune evasion via chemokine sequestration[130]. Given the interconnected nature of the immune system, impacts on cytokine signalling may have downstream impacts on humoral immunity even if the viral proteins have not demonstrated direct effects on B cells.

Viral Fcγ receptors

IgG binding by herpesvirus-infected cells was first reported in 1975 for HCMV, soon followed by a similar observation for HSV-1 and VZV[133–135]. These early findings provided indirect evidence of herpesvirus-expressed glycoproteins capable of binding IgG. Subsequent studies expanded on this observation, leading to the identification of specific genes encoding what became known as viral Fcγ receptors (vFcγRs). These receptors directly bind the Fc region of γ-immunoglobulins and, similar to most immune receptors, are type I transmembrane proteins. However, unlike classical immune receptors, vFcγRs lack signalling motifs and instead contain cytosolic sorting motifs. A major function of these molecules is their ability to interfere with host FcγR activation, making them immunoevasins[58]. In alphaherpesviruses, the vFcγR is composed of a heterodimeric glycoprotein complex formed by gE and glycoprotein I (gI); however, VZV gE can also form homodimers and bind IgG independently[136–138]. Notably, and unlike the HCMV vFcγRs, these glycoproteins also play major roles in cell-to-cell spread[139] and neuropathogenesis[140]. The presence of the vFcγR on virally infected cells directly protected infected cells from ADCC: gE-deficient virus was unable to evade ADCC that was mediated by either a human monoclonal antibody or human sera[137]. Moreover, unmodified HSV-1, but not a gE variant deficient in IgG Fc binding, evaded both human IgG-mediated complement activity and ADCC in a murine flank model of infection[141], demonstrating that the vFcγR is capable of blocking both antibody-dependent complement activation and ADCC in vivo. The vFcγR exists as a heterodimer of gE and gI on the surface of infected cells[134,142] and on the virion surface itself[143]. Together, gE–gI acts as a higher affinity Fc receptor capable of binding to monomeric human IgG[144,145]. HSV-1 gE alone can bind to IgG aggregates, such as antibody–antigen complexes, and acts as a lower-affinity Fc receptor[145]. This IgG Fc binding aids in HSV humoral immune evasion, but the exact mechanism behind the vFcγR-mediated humoral immune evasion by HSV is incompletely understood.

It has been postulated that the vFcγR can mediate immune evasion through the shielding of viral epitopes[146] and the direct blocking of Fc-mediated effector functions[141,147,148]. Given the relatively high affinity of the vFcγR for human IgG and the high concentration of IgG in sera, it is possible that the virion could be coated with IgG, reducing access of neutralizing antibodies to block viral infection, an idea that is supported by evidence from the HCMV field[149]. Another potential mechanism of humoral immune evasion is antibody bipolar bridging (ABB), which occurs when the Fab domain of the antibody molecule is bound to its target envelope glycoprotein while the vFcγR binds to the Fc region[147,150,151]. The presence of a YXXΦ motif on the cytoplasmic tail of gE indicates that this ABB complex present on the surface of virally infected cells could be endocytosed, pulling HSV-specific antibody bound to antigen from the surface of infected cells[152] (Fig. 6). Due to the reduced affinity of the vFcγR for the Fc of IgG at low pH[153], it is likely that these complexes are trafficked to lysosomal-like structures where IgG is released and subsequently degraded[154]. The vFcγR may be recycled back to the surface of infected cells, enabling the continuous degradation of IgG and, thus, evasion of antibody-based immunity. Additionally, it has been proposed that either ABB or vFcγR–Fc interactions block access to FcγRs and/or C1q, thus providing a means to evade Fc-dependent antibody effector functions[148,150]. However, it has also been reported that non-HSV-specific IgG Fc can serve as a bridge linking natural killer cells to HSV-1-infected cells and could protect mice, suggesting that co-engagement of both FcγRs and the vFcγR is possible[155]. Limitations to our mechanistic understanding of vFcγR biology include the fact that the vFcγR cannot bind to murine IgG, making dissection of vFcγR-mediated immune evasion difficult in mouse models[156]. The HSV-1 vFcγR also discriminates between allotypes of IgG1 and IgG3 in humans[157,158], suggesting that differential susceptibility to the vFcγR could impact disease outcomes. Individuals with IgG1 allotypes to which the HSV-1 vFcγR has higher affinity may be more susceptible

for disease as their IgG1s could be more easily scavenged by the vFcγR present on the surface of infected cells[153,159,160]. The opposite may also be true – individuals with IgG1 and IgG3 allotypes that are insensitive to vFcγR activity may be more resistant to infection and more effectively control viral reactivation. Taken together, these studies suggest that improved understanding of the humoral immune evasion mechanisms of the HSV vFcγR has direct implications for developing HSV vaccine and antibody-based therapeutics.

HCMV is unique in that it encodes not one but four IgG binding proteins: gp34 (encoded by *RL11*), gp68 (encoded by *UL119/118*), gp95 (encoded by *RL12*) and gpRL13 (encoded by *RL13*)[161]. All of the HCMV vFcγRs are type I membrane glycoproteins expressed on the infected cell surface, but unlike the others, gp95 is not incorporated into the virion[162]. Also unique to HCMV is that the only known function of each of these proteins is their immune evasion function, with the exception of gpRL13, which has demonstrated additional functionality in repressing HCMV replication in vitro[163]. gp34 and gp68 bind to all human IgG subclasses in a glycan-independent manner, whereas gp95 cannot bind IgG3 and IgG4 (ref. 162). Similar to the HSV-1 vFcγR, these are thought to function through ABB for capturing HCMV-specific antibodies and then mediating internalization via endocytosis, but there is some uncertainty about what occurs next. Similar to host FcγRs, the factor determining whether the IgG is recycled for virion decoration or degraded in lysosomes, the two known fates of IgG bound by these receptors, may be whether the IgG is bound in an immune complex[162]. A recent study found that lysosomes degrade the IgG internalized by gp68 in a transfected cell system, but another study found that only a fraction of internalized Fc fragment associated with gp68 reaches lysosomes in HCMV-infected cells, so these molecules are not degraded in this manner[151,162].

gp34 and gp68 each bind to different regions of the Fc region of IgG and can bind simultaneously, with gp68 acting as the inhibitor of host FcγR recognition through ABB in concert with gp34 enhancing immune complex internalization[164,165]. A broader role in dampening B cell responses has recently been described for gp34 through interaction with the B cell receptor of IgG$^+$ B cells, resulting in a hyporesponsive state in which B cells expressing IgM and IgA as well as IgG fail to respond to T cell-dependent stimuli[166]. gpRL13 is a structural envelope glycoprotein[167], which has been shown in some studies to internalize IgG[163,168]. However, in another study, after mutation of *RL13* to hinder functional production of gpRL13, internalization still occurred as normal, which indicates that this protein may not be necessary for Fc internalization events[162]. Unlike the other three vFcγRs, gp95 has not been conclusively demonstrated to be a virion envelope component or structural protein beyond detection in mass spectrometry data from only one strain[162,167], making it unlikely to be involved with decoration of the viral envelope with IgG. As gp95 is not on the surface of the virus, it is understudied and its role is not completely understood. However, one study showed that rendering gp95 non-functional had no effect on the internalization of IgG, indicating that gp95 is not required for this to occur[162].

The RL11 gene family contains most of the identified vFcγRs along with other immune evasins, but many of these genes, such as *RL13*, are expendable in vitro[163,169]. Thus, there is a need to study these proteins in vivo in order to fully understand their functions and role in pathogenesis. Due to the high species specificities of herpesviruses, animal models carry substantial limitations in translatability[45]. MCMV, for example, is known to express a vFcγR (encoded by *fcr-1*), but similar to the HSV gE protein, performs other roles besides immune evasion[170–174]. However, recent advances in rhCMV have made studying vFcγRs much more feasible with the identification of three vFcγR homologues, Rh05, Rh152/151 and Rh173, which appear to correspond with gp34, gp68 and gp95, respectively[175]. Rh13.1, the rhCMV orthologue to gpRL13, did not demonstrate binding to IgG[175]. The availability of an animal model with strong similarities to humans and closely related CMVs enhances our ability to study these proteins whose functions are best observed in vivo.

Strategies to overcome herpesvirus immune evasion for vaccine development

Effective vaccines often elicit robust antibody responses that can prevent or aid in controlling infection to prevent disease. Furthermore, passive immunization through infusion of potent antibodies has been shown to be a safe and potentially effective strategy for treatment and prophylaxis for infections. Thus, evasion of humoral immunity represents a major challenge to overcome both active and passive vaccine development for herpesviruses, particularly because these viruses employ multiple different mechanisms to evade humoral immunity.

Cell-to-cell spread, entry glycoprotein diversity, glycan shielding and viral diversity are all characteristics that largely impact the neutralizing antibody response and are difficult to address in vaccine design. Yet improved understanding of the mechanism(s) and glycoprotein epitopes involved in cell-to-cell spread and the specific interactions between viral and cellular proteins will enable more targeted strategies for prevention of this key mode of viral dissemination. For example, a newly identified antigenic domain of the HCMV gB protein, antigenic domain 6 (AD-6), has been implicated in mediating cell-to-cell spread, and antibodies targeting this domain are particularly effective in preventing cell-to-cell spread. Responses against this domain may have played a role in the partial efficacy observed in multiple phase II trials of the gB/MF59 vaccine as responses to AD-6 were elicited in the majority of vaccinees[116,176].

Furthermore, sterilizing immunity, which requires neutralizing antibodies to completely prevent infection and/or block virus replication, may be neither an attainable nor a necessary goal of vaccine development for herpesviruses due to these immune evasion strategies. The US Food and Drug Administration (FDA)-approved whole virus varicella vaccine is a key example of this as the vaccine is highly efficacious in preventing acute disease in the form of varicella, but vaccinees are not fully protected against acquisition of wild-type VZV, which can establish latency and reactivate to cause shingles later in life[177–179]. Another example from veterinary medicine is Marek's disease virus (MDV), an alphaherpesvirus which affects chickens through infection of lymphoid tissues leading to immunosuppression. Several live-attenuated whole virus vaccines have been developed and utilized in agriculture for control of MDV, and they are generally effective in preventing serious disease, despite not eliciting sterilizing immunity[180]. The cell-associated nature of this virus, similar to other herpesviruses, is thought to be a major contributor to this observation, leading to an emphasis on cell-mediated immunity in further optimization of vaccination strategies for this virus[180].

The primary approach to addressing glycoprotein diversity has been to utilize whole virus formulations or introduce additional antigens into vaccine candidates[181,182]. However, inactivated whole virus preparations will not elicit immunity against proteins not included in viral particles, so some replication, such as in a disabled infectious single-cycle platform, would be required to elicit responses against non-structural proteins. For other targeted vaccine platforms, the

options for choosing vaccine antigens and sequence variants to include in a vaccine are numerous for viruses as large as herpesviruses, but there are limitations to the number of antigens and quantity that can realistically be included in vaccines using platforms such as recombinant protein or mRNA. The development of neutralizing antibodies has been the primary goal of many vaccines in development, but evidence in the HCMV field implicates Fc-mediated antibody effector functions in protection from HCMV-associated disease, such as congenital infection and HCMV viraemia post transplant[61,62,183]. Thus, mapping humoral responses to identify prominent targets of Fc-mediated antibody effector functions could inform vaccine development by narrowing the options for target antigens with greater potential to elicit protective responses.

Glycan shielding represents a challenge in vaccine development because the same glycans that decorate viral proteins are also utilized by host proteins[184]. Glycan targeting has been effective in vaccines against bacteria[185] but with limited success thus far for antiviral vaccines, although significant efforts towards this have been made in the HIV field[106]. Re-designing vaccine antigens to allow the immune system to access key epitopes may yield limited success in improving efficacy as these epitopes are largely hidden due to the glycan shield during natural infection. B cell lineage approaches and selective deletion and reintroduction of N-linked glycosylation sites, similar to those in development for HIV, may be a way around non-immunodominant protective epitopes. Initial immunization utilizing a glycan mutant to expose the epitope of interest on the target antigen initiates the B cell response and driving B cell lineages that can accommodate the glycan in the epitope by adding the glycan back to subsequent immunizations[186].

Viral immune evasion proteins represent promising vaccine antigen candidates for boosting antiviral immune function. Targeting viral cytokines may lead to broad effects on the immune response due to the downstream signalling cascade and because many cytokines perform different functions on different cell types, but these proteins are largely recognized as modulators of innate and T cell immunity, with potential indirect effects on the development of humoral immunity[117,118,187]. For example, one study investigating rhCMV vIL-10 as a vaccine immunogen demonstrated that animals with strong anti-vIL-10 antibody responses were slower to seroconvert to non-vaccine antigens when exposed to actively shedding monkeys compared with animals with weak responses or immunized only against gB. However, general rhCMV-specific antibody responses were less durable in the strong responders to vIL-10 with a much more drastic drop off in rhCMV binding antibodies following peak immunity[188]. We have only just scratched the surface of investigating these immune modulators in the context of vaccine development, but because some viral cytokines and decoy receptors carry notable sequence and structural homology with their host counterparts[187], care must be taken to ensure autoimmune responses are not induced by vaccination with these proteins before considering them in vaccine candidates.

Alternatively, herpesvirus vFcγRs specifically aid in evasion of Fc-mediated effector antibody responses and are distinct from host FcγRs, and there are several potential options for reducing the impact of vFcγR-mediated immune evasion. Early vaccines against VZV for prevention of shingles were live-attenuated whole virus formulations, but a new recombinant vaccine was licensed in 2017 by the FDA for prevention of shingles. Shingrix contains VZV gE adjuvanted with the T cell boosting adjuvant $AS01_B$ and has consistently demonstrated strong efficacy in prevention of shingles, but the exact mechanism of protection is still unclear as the gE–gI protein complex plays several important roles in VZV infection in addition to its potential role in immune evasion as a vFcγR[14,16,189,190]. Beyond the impact on immune evasion, directly targeting the vFcγRs of alphaherpesviruses, such as HSV-1 and HSV-2, may have additional benefits due to the multifunctionality of these protein complexes. The pathobiology of these vFcγRs has begun to be explored in the context of antibody prophylaxis and therapy. Because the HCMV vFcγRs bind at different locations on Fc from each other and host FcγRs, engineering the Fc domains of therapeutic monoclonal antibodies to disrupt the vFcγR binding while maintaining the ability to engage host FcγRs is a feasible strategy being explored for developing passive immunization strategies for HCMV. However, HCMV gp68 and HSV gE–gI are known to bind Fc at the CH2–CH3 interdomain hinge, which is the same binding site at the neonatal Fc receptor (FcRn), which is important for IgG recycling, the transfer of IgG across barrier tissues and antigen presentation[165,191,192]. Thus, altering interactions with these vFcγRs may impact FcRn affinity and subsequent ability of the antibody to persist in serum and to infiltrate tissues, in addition to potential off-target effects on effector functions[193]. However, an early report suggests that, at least for HSV, these activities may be separable: a gD-specific antibody engineered for better binding to human FcRn exhibited loss of vFcγR binding, improved neutralization activity in vitro and enhanced in vivo protection in a mouse model of HSV infection[194]. In the meantime, other promising strategies currently under investigation are to directly target the vFcγRs via active vaccination or passive immunization of monoclonal antibodies specific for the active site of a vFcγR.

An additional consideration in the development of vaccines and immunotherapeutics for herpesviruses is the potential differences in immunity needed for prevention of acute disease and disease associated with reactivation or secondary infections. For instance, the VZV vaccines licensed for prevention of varicella are live-attenuated whole virus vaccines, whereas the shingles vaccine is a protein subunit vaccine[195]. Although VZV is the only human herpesvirus with licensed vaccines, we speculate that broader responses are necessary for prevention of disease associated with primary infection, whereas a more directed response is needed for prevention of viral reactivation. This may be especially of interest when considering targeting viral immune evasins as the roles and relative importance of these proteins may differ across phases of infection.

Conclusions

Human herpesviruses cause lifelong infections and are extremely prevalent globally; they represent a massive overall burden of disease, including serious implications for infected newborns and individuals experiencing immunosuppression, as well as an increased risk of associated malignancies and neurodegenerative disease. Immunity elicited by natural infection is not completely protective against these outcomes[196–198], so the challenging goal of vaccine development for several herpesviruses has been to elicit immunity that is superior to that elicited by natural infection. However, these large DNA viruses utilize many mechanisms to subvert every aspect of the immune response from innate to adaptive immunity. Herpesviruses evade humoral immunity through mechanisms of cell-to-cell spread, glycoprotein diversity within and among virus strains, glycan shielding and expression of proteins that directly modulate the immune response, including viral cytokines, cytokine receptors and Fc receptors. Targeting or circumventing these immune evasion mechanisms may be the key to achieving immunity beyond what is elicited by natural infection. However, research is limited by translatability of animal models due to the high

species specificity of herpesviruses, so there are currently gaps in our understanding of the specifics of many of these mechanisms and in vivo function that limit the application to immunization strategies.

Although addressing humoral immune evasion by any one of the proposed strategies has potential for improving the efficacy of immunotherapeutics and vaccines against herpesviruses, successful herpesvirus immunization may require a combination of innovations to induce effective humoral immunity as well as activation of appropriate T cell responses to finally achieve the efficacy needed to end the silent epidemics of herpesvirus-associated diseases. Furthermore, different strategies may be needed in different phases of infection given that pathology can differ among acute infection, chronic infection, superinfection and reactivation. Antibodies are important for prevention of acquisition of herpesviruses and transmission given that they can act on free virions and cell-associated virus. Yet sterilizing immunity is likely an unattainable standard for prevention of herpesvirus-associated disease and may explain the only minimal or partial efficacy of clinical vaccine trials in which the primary end point has been prevention of acquisition in naive individuals. On the other hand, prevention of herpesvirus-associated disease more broadly will almost certainly require induction of multiple arms of the immune system, including B cells, T cells and bridging innate-to-adaptive immune functions to work in concert for prevention or amelioration of herpesvirus-associated disease. The immune evasion mechanisms presented here focus on those that affect humoral immune function, but herpesviruses are adept at evasion across all arms of the immune system. Targeting these immune evasion strategies may be a pathway to improve on the partial efficacy of vaccine strategies to reduce herpesvirus infection and associated disease.

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Author contributions

C.E.O., M.D.S., L.M., A.R. and P.K. researched data for the article. C.E.O., M.D.S., M.E.A. and S.R.P. contributed substantially to discussion of the content. C.E.O., M.D.S., L.M., A.R. and P.K. wrote the article. C.E.O., M.D.S., P.K., M.E.A. and S.R.P. reviewed and/or edited the manuscript before submission.

Competing interests

S.R.P. has served as a consultant to Moderna, Pfizer, Dynavax, Kamada, Imunon and Merck, and has led sponsored programmes with Moderna, Pfizer, Dynavax and Kamada. M.E.A. has a sponsored project with Moderna and patents/applications related to antibody-based interventions against neonatal herpes simplex virus (nHSV) infection. P.K. serves as a consultant to Oak Hill Bio and had a sponsored project with Biotest AG (2022–2024). These activities had no impact on this article. The other authors declare no competing interests.

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