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REVIEW

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Characteristics of herpes simplex virus infection and pathogenesis suggest a strategy for vaccine development

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Summary

Herpes simplex virus (HSV) can cause oral or genital ulcerative lesions and even encephalitis in various age groups with high infection rates. More seriously, HSV may lead to a wide range of recurrent diseases throughout a lifetime. No vaccines against HSV are currently available. The accumulated clinical research data for HSV vaccines reveal that the effects of HSV interacting with the host, especially the host immune system, may be important for the development of HSV vaccines. HSV vaccine development remains a major challenge. Thus, we focus on the research data regarding the interactions of HSV and host immune cells, including dendritic cells (DCs), innate lymphoid cells (ILCs), macrophages, and natural killer (NK) cells, and the related signal transduction pathways involved in immune evasion and cytokine production. The aim is to explore possible strategies to develop new effective HSV vaccines.

KEYWORDS

Herpes simplex virus, immunity, vaccine

1 | INTRODUCTION

Herpes simplex virus (HSV) belongs to the alpha subfamily of the human herpesvirus family and includes HSV1 and HSV2, which are responsible for pandemics of various herpes diseases.[1] Both pathogens have similar structural characteristics and are of concern worldwide, not only because the clinical outcome of oral or genital ulcerative lesions has long-lasting impacts on patient quality of life but also because ocular herpes can lead to blindness, and neonatal herpes or encephalitis can result in higher death rates.[2-4] In addition, the viruses show higher infection rates in various age groups.[5] Although observations of epidemics in various areas have described different pandemics, infection rates of at least 30% to 60% for HSV1 and 10% to 25% for HSV2 have been recognized by most researchers,[6,7] and approximately 23 million new cases of HSV2 infection are reported annually.[8] It is not surprising that a viral disease with such severe clinical outcomes and such a strong spreading trend has been targeted for prophylactic vaccine development. To date, more than 10 HSV prophylactic vaccines, mainly vaccines targeting HSV2, have been developed and evaluated in human clinical trials.[9,10] These

Abbreviations: CCR7, C-C motif chemokine receptor 7; cGAS, cyclic GMP-AMP synthase; CTL, cytotoxic T lymphocyte; CXCR4, C-X-C motif chemokine receptor 4; DC, dendritic cell; Grb2, growth factor receptor bound protein 2; HCF-1, host cell factor 1; HS, heparin sulfate; HSV, herpes simplex virus; HVEM, herpes virus entry mediator; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; ISG, interferon-stimulated gene; MHC, major histocompatibility complex; NK, natural killer; Oct-1, octamer-binding transcription factor 1; PAMP, pathogen-associated molecule pattern; PDCD4, programmed cell death 4; PILR, paired immunoglobulin-like type 2 a receptor; PRR, pattern recognition receptor; PVRL, poliovirus-receptor-like; RIG-1, retinoic acid inducible gene-I; RLR, RIG-I-like receptor; TLR, toll-like receptor; TNF, tumor necrosis factor

TABLE 1 Development and status of herpes simplex virus (HSV) vaccine candidates

Candidate Type	Name	Description	Preclinical	Phase I	Phase II	Phase III
Live attenuated vaccine	HSV1-Tat[13]	HSV1 encoding the HIV-1 Tat protein	*			
	HSV1 VC2[14]	Mutated with the gK and UL20	*			
	HSV2 ▵NLS[15]	HSV2 ICP0⁻ virus, 0ΔNLS	*			
	HSV2 ▵gD2[16]	Deleted in gD	*			
	AD472[17]	Deleted both copies of the γ134.5, UL55-56, UL43.5, and the US10-12 region	*			
Subunit vaccine	HSV2 gD[12]	gD with alum and 3-*O*-deacylated monophosphoryl lipid A				*
	HSV2 gB/gD/MF59[18]	gB and gD with MF59				*
	HSV1 VP11/12[19]	$VP11/12_{66\text{-}74}$, $VP11/12_{220\text{-}228}$, and $VP11/12_{702\text{-}710}$	*			
Replication-defective	HSV2 529[20]	Deleted in UL5 and UL29		*		
	HSV1 d120[21]	Deleted in ICP4	*			
	HSV1 d92[21]	Deleted in ICP4 and ICP27	*			
	HSV1 d95[21]	Deleted in ICP4, ICP27, and ICP22	*			
	HSV1 d97[21]	Deleted in ICP4, ICP27, and ICP0	*			
	HSV1 $vhs^{-}/ICP8^{-}$[22]	Deleted in Vhs and ICP8	*			
DNA vaccine	pRSC-gD-IL-21[23]	HSV1 gD combined with IL-21	*			
	gD-based polynucleotide vaccine[24]	Codon optimized and ubiquitinated HSV2 DNA vaccine based on the gD			*	
	Vaxfectin(®)-gD2/UL46/UL47[25]	gD2/UL46/UL47 formulated with an adjuvant Vaxfectin(®)			*	

vaccines contain antigens that effectively stimulate immune responses and immune memory, as measured by the indicators of neutralizing antibody and specific cellular immune responses in animals or humans.[11,12] These data suggest that the viral antigens selected and designed for vaccines are effective and that the host immune system is capable of recognizing HSV antigens. However, of the vaccines that have undergone evaluation in a clinical trial, none except a vaccine against HSV2 that showed only low efficacy for HSV1 infection but did not work against HSV2 infection has demonstrated sufficient efficacy for further development or commercialization (Table 1).[11] On the basis of these results, we hypothesize that the evaluations currently used in HSV vaccine development, in which antiserum from immunized individuals blocks virus infection in cells in classic neutralizing antibody assays and antigenic peptides from viral surface molecules specifically induce the proliferation of interferon γ (IFN-γ) secreting T cells in enzyme-linked immunospot (Elispot) assays, might not fully and accurately represent an immune response that enables the control of HSV infection. Both classic assays show that neutralizing antibodies block virus entry into a single type of cell, usually epithelial cells or fibroblasts,[26] and Elispot assays reveal only the capacity to develop a CD4 or CD8 T-cell immune response to limited antigens mainly located on the viral surface.[27] Furthermore, it is reasonable to infer that the immunity induced naturally in most individuals infected by HSV might be incomplete or weakly effective on the basis of the observation that most infected individuals seem to be unable to clear the virus completely in their lifetime.[28] If this is the case, we must ask how the virus interacts with the immune system during its infectious process and leads to an abnormal immune response, which might produce specific antibodies against only viral surface proteins. The accumulated research data concerning the interactions of HSV and host cells and the associated pathogenic mechanisms can help us to answer this question. In these works, the HSV genome was revealed to possess a large amount of genetic information and a complicated transcription mechanism[29] and to encode various functional molecules,[30] which enable interactions with the cellular microenvironment in a systematic and sequential manner to facilitate pathogenesis.[31,32] Although this process is basically similar to that of some RNA viruses with simple structures that expose their inner pathogen-associated molecule patterns (PAMPs) to cellular pattern recognition receptors (PRRs) in infected cells and activate the NF-κB transcription pathway of innate immunity,[33] HSV possesses various encoded molecules that are not only recognized by PRRs but also used to block or regulate the PRR signal transduction pathways that activate NF-κB.[34-36] This feature might be predicted to lead to a deviation in signal transduction during the innate immune response, which usually involves the activation of innate immune cells, including dendritic cells (DCs), innate lymphoid cells (ILCs), macrophages, and natural killer (NK) cells.[37-39] This activation can be understood as a broader response than the immune response elicited during HSV infection, which appears to produce specific humoral and cellular responses against only viral surface structures recognized by the innate immune system during the early stages of infection. Our previous understanding of HSV vaccination depended on the observation of clinical immunological data from viral infection or disease and might not support the development of a new generation of HSV vaccines. Further analysis of the mechanism by which HSV interacts with the host and the pathogenic effects of HSV on the immune system will be helpful for our efforts to develop HSV vaccines. In this review, we discuss the available data concerning

the interplay of HSV and the host immune system and investigate a possible pathway for HSV vaccine development.

2 | THE STRUCTURAL CHARACTERISTICS OF HSV DETERMINE ITS STRATEGY FOR INTERFERING WITH HOST DEFENSE

A previous description of HSV indicated that the genomic lengths of the virus types were 152 201 bp for HSV1 (strain McKrae)[40] and 154 746 bp for HSV2 (strain HG52),[41] and these genomes could encode at least 80 proteins, in addition to some RNA molecules. Among these proteins, approximately 20% were found to directly support viral replication,[42] 12% were immunogenic surface glycoproteins,[43] and more than 50% were involved in interactions with the host and indirectly supported virus survival in vivo.[44] The existence of these kinds of protein in HSV, which has coevolved with humans for a long time, suggests not only that viral pathogenesis involves various interactions of viral molecules with different cells and tissues[45] but also that the virus uses strategies to activate cellular transcription and evade immune monitoring to create an effective environment for viral proliferation.[46] It could be proposed that immune pressure from the host has pushed HSV to fully exploit its genomic evolution by encoding a series of functional molecules and gradually creating different pathways for blocking or weakening innate and adaptive immunity during the continuous interplay between viruses and humans.[28,47] Of note, a recently published paper indicates that the HSV1 0ΔNLS vaccine elicits antibody responses against heterogeneous viral proteins, including nonstructural proteins.[48] However, to some extent, the characterized pathological processes of HSV in infected individuals, including primary acute infection, immune evasion, latent infection, and reactivated infection in neurons, can be viewed as clinical phenotypes that reflect the mechanisms by which viral molecules compete with, interfere with, activate, and hijack host defense. Therefore, investigating the interplay between viral molecules and host factors could improve our systematic understanding of viral infection strategies and inspire new ideas for vaccine development.

2.1 | Interaction of HSV surface glycoproteins with cellular receptors

As an enveloped DNA virus, HSV possesses several typical envelope glycoproteins,[43] which play roles in binding to cellular surface receptors and mediating virus entry into cells.[49] A total of 12 glycoproteins have been found in the viral envelope, and at least five glycoproteins, gB, gC, gD, gH, and gL, have been demonstrated to enable interactions with cellular receptors to promote virus entry.[50] Reported data have suggested that gB can bind to heparin sulfate (HS) on the cell surface and couple to paired immunoglobulin-like type 2 a receptor (PILR)[51] and that gC is also involved in these interactions.[52,53] Interestingly, after gB binds to its receptor, gD is induced to interact with nectin-1 and poliovirus-receptor-like (PVRL1) on epithelial cells or herpes virus entry mediator (HVEM or TNFRSF14) on immune cells,[54] as gD can interact with HS.[55] The binding of gD to receptors also causes the activation of gH/gL and the formation of a complex containing both glycoproteins,[56] followed by increased fusion of the viral and cellular membranes mediated by gB.[57,58] During this process, gC can promote virus entry into cells through binding to cellular proteins.[59] There are also data suggesting that gH/gL plays a more important role in the fusion of viral and cellular membranes and that cellular integrin is a potential receptor for gH/gL.[60] Endocytic vesicles are also a pathway of viral entry into cells.[61] These data suggest that HSV uses a more systematic strategy for entry into cells than most viruses. This strategy involves various surface glycoproteins interacting with different cellular receptors. This process implies that the basic idea of blocking virus entry into cells requires a combination of multiple neutralizing antibodies rather than a few antibodies. Furthermore, the recognition of HVEM by gD leads to viral tropism for various innate immune cells expressing HVEM, including DCs, ILCs, macrophages, NK cells, and even CD8 cytotoxic T cells.[62-65] Thus, HSV is capable of infecting these cells in epithelial tissue after proliferating in epithelial cells and inducing the innate immune response (Figure 1).[33] In light of this evidence, it is reasonable to speculate that the innate immune cells that function in phagocytosis, antigen presentation, and the transfer of stimulatory signals are hijacked and probably adopt a heterogeneous phenotype, leading to the transfer of a heterogeneous signal for the stimulation of adaptive immunity.

2.2 | Biological features and potential immunogenicity of the HSV tegument

Among the HSV structural components, tegument proteins are functional molecules that are located between the viral capsid enveloping the genome and the outer membrane.[66,67] To date, approximately 24 tegument proteins have been identified and found to play important roles in viral structure,[68,69] as they provide supportive functions for establishing an effective microenvironment for viral proliferation during infection.[70,71] Previous reports indicated that the genes encoding seven tegument proteins are conserved between HSV1 and HSV2 and possess high similarity in viruses in the alpha subfamily,[72] suggesting important roles for these proteins in viral evolution. Most tegument proteins form complex structures by interacting with each other and anchoring to capsids or membranes to stabilize the viral structure.[73-75] Topological data suggest that the interactions between tegument proteins and cellular structure may or may not depend upon the myristyl- and palmityl-base anchors produced by posttranslational modifications on the surfaces of these proteins.[76,77] Interestingly, some tegument proteins play important roles through their interactions with cellular molecules, as they are involved in the viral structural network.[68,73] Typically, the tegument proteins Vp16 and Vhs, which are encoded by the ul48 and ul41 genes, respectively, can form a trimeric complex with another tegument protein encoded by ul49 (pUL49-pUL48-pUL41).[78,79] Furthermore, VP16 is thought to reside closer to the viral envelope and be part of the outer

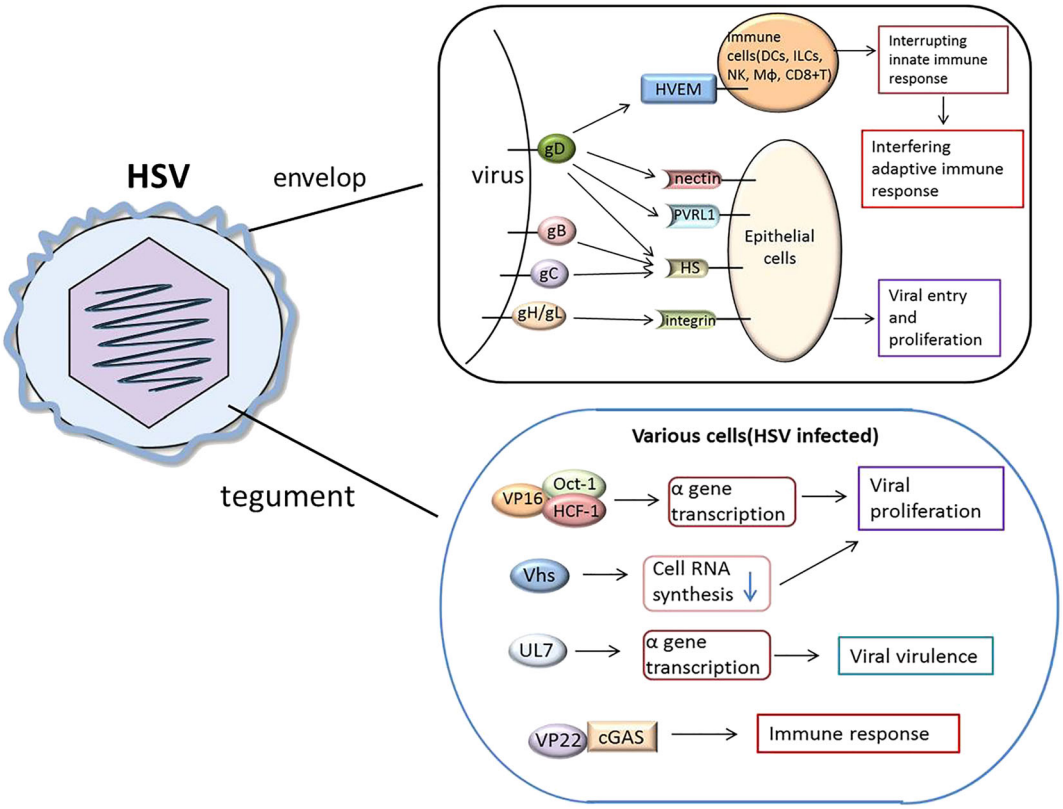

FIGURE 1 Interactions of herpes simplex virus (HSV) surface glycoproteins and tegument proteins with cellular components to interfere with host defense. At least five glycoproteins, gB, gC, gD, gH, and gL, have been demonstrated to enable interactions with epithelial cellular receptors or immune cells to promote virus entry or proliferation or even to disrupt innate and adaptive immunity. In addition, some tegument proteins play important roles, for example, roles in viral proliferation, viral virulence, and host immunity evasion, through interacting with cellular molecules

tegument. VP16 also plays an important role in viral egress downstream of the initial envelopment step.[80] VP16 is also capable of participating in a supporting structure (pUL36-pUL37-pUL48) with two tegument proteins encoded by the ul36 and ul37 genes.[81] However, most investigations of VP16 and Vhs have focused on their biological functions in regulating the transcription of the viral genome and interfering with host RNA synthesis, respectively.[82] VP16 was found to interact with the cellular transcripts octamer-binding transcription factor 1 (Oct-1) and host cell factor 1 (HCF-1) and to initiate transcription of the viral α-gene via a three-component complex, which controls viral proliferation in cells, probably including neurons.[83,84] Vhs plays roles in interfering with host RNA synthesis and providing a space for transcription during viral proliferation.[85,86] Studies have suggested the biological and pathological significance of tegument proteins in viral structure and infection. Importantly, the findings of these studies have also implied that if tegument proteins were recognized by the immune system during infection, the pathological effects of the virus could be limited to some extent; the deletion of some tegument proteins could also be a way to influence viral pathogenesis. A study of the tegument protein UL7 suggested similar results, as the UL7-UL51 complex was found to colocalize with gE in the nuclear region of infected cells.[87] The deletion of the ul7 gene eliminates this colocalization but does not affect viral structural.[88,89] Interestingly, partial deletion of this gene could limit viral proliferation and lead to delayed growth kinetics of the virus in cultured cells or animals because UL7 regulates the transcription of the viral α-gene,[90] and this partial deletion could provide an attenuated viral phenotype (Figure 1).[91] Other studies have also suggested that VP22, which is encoded by the ul49 gene, is capable of interacting with cellular cGAS and inhibiting its enzymatic activity, as VP22 functions in the viral structural network.[70] The tegument proteins encoded by ul16 and ul46 also show capacities to interact with cellular mitochondria and p85, growth factor receptor bound protein 2 (Grb2), and shc of the Src-family kinases, respectively, as part of their roles in the viral structural network.[92,93] These data describe a specific context for HSV infection, in which the viral strategy is to present only surface glycoproteins to the immune system, as most of the pathogenic viral molecules work within infected cells and can avoid monitoring by the innate and adaptive immune systems through various forms of immune evasion.

3 | THE STRATEGY BY WHICH HSV EVADES MONITORING BY THE IMMUNE SYSTEM

Observations from epidemics of HSV infection worldwide suggest a characteristic clinical feature in which a high ratio of serum positivity,

which reaches more than 50% in the population, is associated with viral latency in the nervous system, which can lead to viral reactivation in infected individuals.[7] This process has been demonstrated to be caused by the latent infection of neurons by HSV.[30] On the basis of data from studies of HSV pathogenesis, this conclusion is reasonable. The only uncertainty is whether viral latency, which depends on the process of viral entry into neurons from epithelial tissue, might lose control of the activated innate immune response during viral infection or still retain control because of the strong neurotropic characteristic of HSV.[94,95] Although there are many examples of neurotropic viruses that have the characteristics of intense neurotropism and a shorter proliferative cycle than HSV, a lower rate of neuron infection was observed for these viruses than for HSV.[96] In contrast, neuron infection by HSV is observed in 100% of virus-infected individuals. Thus, it is logical to infer that HSV possesses the capability to interfere with innate immunity, as innate immunity is activated by viral infection in the epithelial tissue of infected individuals.[97] Data from epidemics have also suggested that the high rate of serum positivity in the population does not prevent a high incidence of HSV infection; eg, approximately 23 million new cases of HSV2 infection are reported each year.[8] Thus, the immune response induced in infected individuals, which usually involves specific neutralizing antibody and cytotoxic responses, is not capable of defending against viral reinfection or latent virus reactivation. This viral characteristic is reported to be an immune evasion strategy[98] and is probably due to viral interference with the immune system by various encoded viral proteins.[99] To understand this process, it is necessary to review the details of the interactions between the virus and the innate and adaptive immune systems.

3.1 | HSV infection and the IFN reaction of the host

Studies on antiviral innate immunity have indicated that IFN-α/β and their family members, as defenses against viral small molecules, could be indicators of effective antiviral mechanisms and play important roles in controlling viral spread at primary infection sites through stimulating various cells to express molecules that inhibit virus proliferation.[100,101] Indeed, studies of HSV pathogenesis have suggested that the expression of IFN-α/β or IFN-λ in epithelial cells can be observed,[102] which is related to not only viral surface glycoprotein binding to cell receptors[103] but also viral PAMPs interacting with cellular PRRs as the virus replicates in infected cells. Detection of intracellular viral products by toll-like receptor (TLR), cGAS, RLR, and p204/STING activates signaling pathways resulting in ISG-encoded products as well as driving tetherin expression.[28,104-106] Although this process suggests the activation of the innate immune response during HSV infection, subsequent observations have indicated that this IFN reaction is unable to block viral spread to the target neural tissue, as viral proliferation in epithelial tissue induces vesicle lesions in most infected individuals.[107] Studies of this process suggest that various virally encoded molecules, most of which are tegument proteins, are capable of interacting with different components of the IFN signaling pathway and the NF-κB transcriptional network and interfering with signal transduction and the transcription of IFN mRNA transcripts. The viral immediate gene product ICP0 was found to be capable of blocking the translocation of the DNA-binding protein p65 to the cell nucleus in the NF-κB pathway and promoting the enzymatic proteolysis of p50, which possesses a function similar to that of p65.[108,109] On the other hand, ICP0 was found to be capable of interacting with the IFI16 protein and down-regulating its phosphorylation to assist cGAS in sensing viral double-stranded DNA (dsDNA) during viral genomic replication, which could interfere with signal transduction in the IFN pathway.[110] The HSV tegument protein Us3 was observed to inhibit the activation of NF-κB by superphosphorylating p65 in virus-infected cells and to block the translocation of superphosphorylated IRF-3 into the nucleus, which could directly inhibit IFN production.[111] This process could be involved in the variations in either inflammatory factors and/or chemokines during HSV infection.[112] Other virus-encoded proteins, such as ICP27, enable the inhibition of NF-κB by interacting with IκBα,[113] and UL42 inhibits NF-κB activity by interacting with the p65/50 complex and retaining this complex in the cytoplasm.[114] The tegument protein VP16 interacts with p65 and represses NF-κB while interfering with the binding of CREB to the IRF-3 complex to block the IRF-3 transcriptional process.[115] Another tegument protein, Vhs, binds to the mRNAs of IFN-stimulated genes to promote their degradation and leads to reduced antiviral activity of IFN members.[85] An important viral protein, γ-34.5, targets TBK1 to block its interaction with IRF-3 and repress IFN production,[116] and viral VP24 interacts with both TBK1 and IRF-3 to block signal transduction and repress IFN expression.[117] These observations provide extensive evidence that HSV interferes with IFN production (Figure 2). These data demonstrated that an innate response that relies on IFN might not restrain the neurotropic spread of HSV from primary infected epithelial tissues to neurons. It should be stressed that various immune signals, such as tumor necrosis factor (TNF) members and cytokines including interleukins (IL-1, IL-4, IL-13, IL-17, IL-22, and IL-33), which could play important roles in the activation of various innate immune cells and are regulated by the NF-κB transcription system, are equally crucial for IFN production.[118-120] Thus, the signaling network that activates and regulates processes in the innate immune system during the initial response to HSV infection can be disrupted by virus-encoded molecules.

3.2 | HSV and host apoptosis during infection

In mammals, apoptosis is capable of maintaining homeostasis in normal tissues,[121-123] which means that apoptosis is involved in defending against viral infection, as it is triggered by stimuli during lytic viral infection.[124] Apoptosis is involved in the disruption of mitochondrial membrane integrity, which releases cytochrome c into the cytoplasm.[125] Importantly, Bcl-family members, including Bcl-2, Bcl-w, Bcl-x_L Bax, Bak, Bad, Bid, Bim, Bik, Noxa, and PUMA, exert

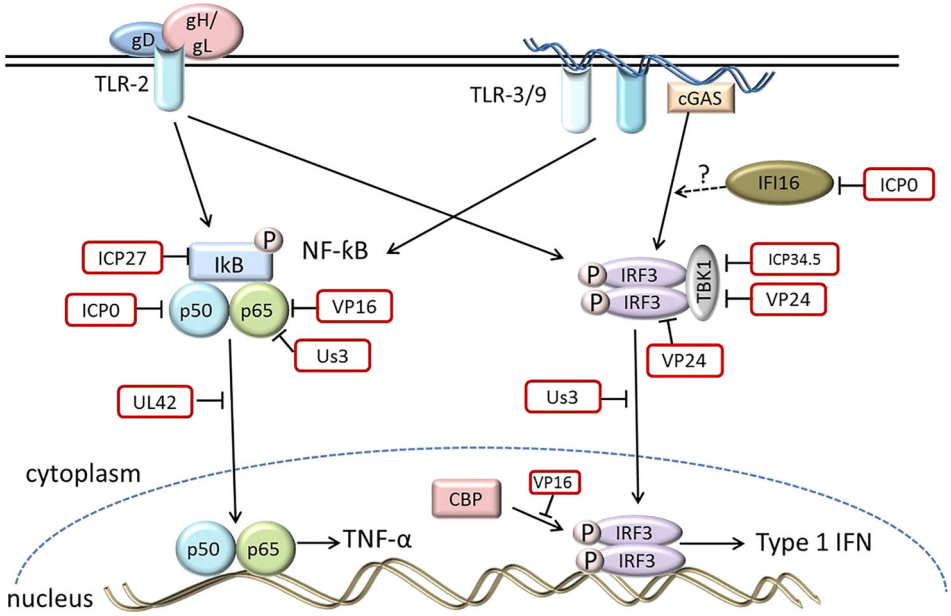

FIGURE 2 Evasion of the IFN-I signaling pathway by HSV1. Cellular receptors or sensors, such as TLR-2, TLR-3, TLR-9, and cGAS, recognize glycoproteins or double-stranded DNA and trigger IFN-I production through the transmission of a series of signals. Multiple steps in the IFN-I signaling pathway can be targeted by HSV1 proteins. CBP, CREB-binding protein; P, phosphate

proapoptotic or antiapoptotic effects to regulate and integrate this physiological process.[126-128] In theory, apoptosis should limit HSV proliferation in the cell nucleus, as this process requires more than 18 hours at the primary infection site during the early stage of infection. However, this innate defense mechanism does not effectively repress viral spread from infected epithelial cells to neurons or other tissues, even if apoptotic cells are detectable.[124] Previous data have suggested that the immune evasion strategy used by HSV during infection depends to some extent on its antiapoptotic mechanism.[129] Studies have shown that soluble viral gD activates the NF-κB, Akt, and ERK1/2 signaling pathways in macrophages and prevents apoptosis triggered by staurosporine. gD is also capable of preventing apoptosis in U937 cells triggered by anti-Fas antibodies.[130,131] Further investigation has shown that this antiapoptotic effect of gD is associated with the upregulation of the expression of the Bcl-2 and Bcl-xl genes, which both encode antiapoptosis proteins, and downregulation of the expression of the Bcl-xs gene, which encodes a protein that promotes apoptosis.[132] The mechanism of this process might involve cellular cyclophilin, which is capable of triggering apoptosis, its receptor HS, and signaling pathways associated with the Akt and ERK1/2 complex. Interestingly, HS has been shown to be bound by viral gD. Many studies have focused on the main apoptosis regulator of HSV during infection, the viral serine/threonine protease Us3, and found that the virus is capable of modulating the apoptotic process on the basis of its requirement for cell proliferation during infection.[133] Us3 can mediate the posttranslational modification of the Bad protein, which negatively regulates apoptosis through its kinase activity, and block protease A to activate some apoptotic signals via the prephosphorylation of protease A.[134] The data also suggest that Us3 can interact with the apoptosis-related protein programmed cell death 4 (PDCD4) to block the initiation of apoptosis in infected cells.[135] Us3 enables the attenuation of JNK activity, which assists with the activation of apoptotic signals in a state of cellular stress.[136] This capacity was confirmed in a study with a Us3-deficient strain.[137] On the other hand, the viral protein Us5, which is also named gJ, is encoded in a multigene open reading frame with Us3 and is capable of preventing apoptosis triggered by an anti-Fas antibody.[138] Interestingly, the viral immediate protein ICP27 is able to promote or inhibit apoptosis depending upon the infectious background.[139,140] These data suggest that HSV possesses a set of mechanisms for regulating apoptosis to proliferate in primary infectious sites and spread to various tissues and cells, especially neurons; preventing or enhancing apoptosis could be part of this viral strategy. Importantly, host apoptosis works to control viral spread and initiate the phagocytosis of dead cells and viruses by the innate immune system,[141] which contributes to innate immunity and activates adaptive immunity. The HSV strategy for effectively regulating apoptosis might lead to abnormal progression from innate to adaptive immunity.

3.3 | Infection of immune cells by HSV and the pathological significance

The infection of some immune cells is an important pathological feature of HSV that leads to a negative effect on the antiviral immunity induced by the virus and represents a challenge for HSV vaccine development. Previous data have confirmed that the viral infection of peripheral DCs induces vesicle lesions in the skin or mucosa and have suggested the virus impacts the transduction of antigen signals from the innate immune system to the adaptive immune system via

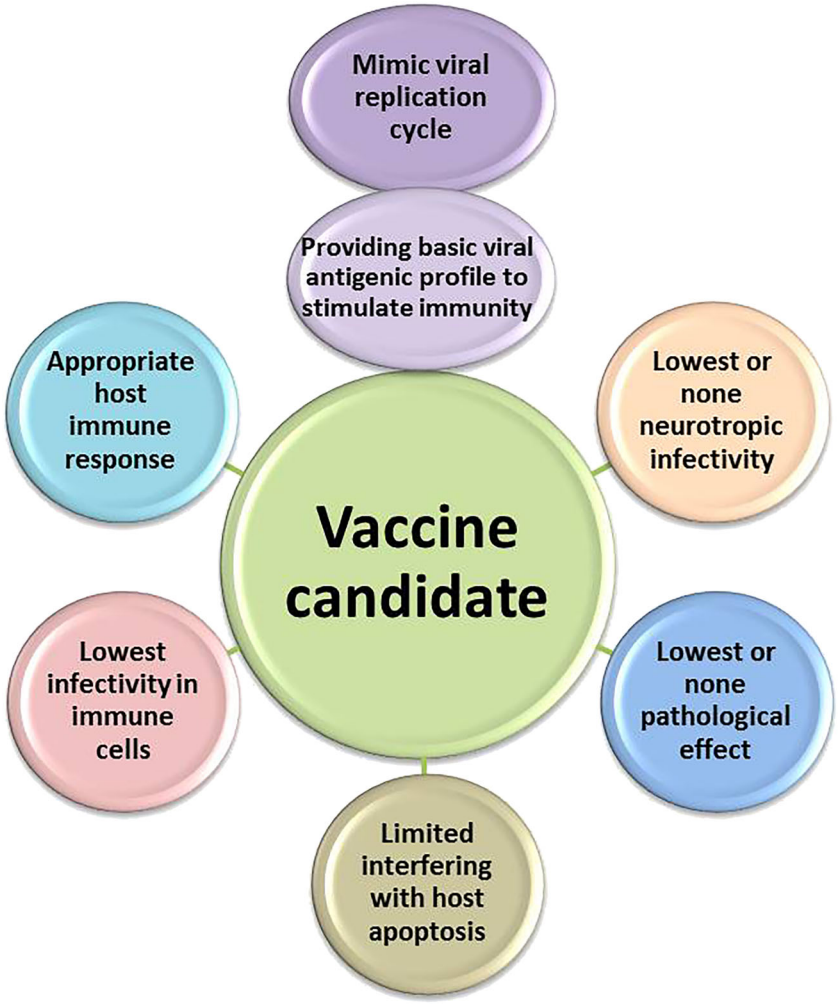

FIGURE 3 Tactics for herpes simplex virus (HSV) vaccine development. The design of HSV vaccine candidates would be required to achieve at least six objectives including viral replication cycle mimicry, appropriation of the host immune response, lowest infectivity possible in immune cells, limited interference with host apoptosis, lowest possible or no pathological effect, and lowest possible or no neurotropic infectivity

classic antigen presentation. These studies observed that the expression of some coactivating immune molecules, including CD1a, CD40, and intercellular adhesion molecule 1 (ICAM-1), on the surface of HSV-infected DCs is limited, while the expression of other DC surface molecule, including CD83, C-C motif chemokine receptor 7 (CCR7), C-X-C motif chemokine receptor 4 (CXCR4), and IFNGR1, was downregulated during the transition of infected immature DCs into a mature state.[142-144] Thus, infected DCs might present variable immunological phenotypes during their transition from a physiologically immature state to a mature state. On the other hand, viral infection might induce damage to the DC membrane and lead to the release of immune signals and spreading of virus. This event might cause not only further viral infection of other cells but also abnormal immune signaling in various immune cells, which could reshape the immune response. Further study of infected DCs has revealed that the transfer of antigen from the cytosol to the endoplasmic reticulum is blocked by HSV infection, which could downregulate antigen presentation to T cells by DCs through restricting the binding of antigen to the major histocompatibility complex 1 (MHC-1) molecule in cells.[144] The data have also suggested that HSV is capable of interacting with caveolin-1 to alter the activity of nitric oxide synthase and limit the production of NO[145] and that the migration rate of infected DCs moving from the local tissue to the lymph nodes was decreased because of an increased death rate.[142] All of these data suggest the hypothesis that by interfering with DCs, a major antigen-presenting cell in the immune system, HSV infection might lead to abnormal immune signaling in T cells and induce weakened adaptive immunity. Our unpublished work suggests that HSV infection of ILCs located in epithelial tissue can modify the ILCs phenotype. Both DCs and ILCs are functional cell subsets that link the innate and adaptive immune systems by interacting directly with T cells and/or presenting antigens to them. Viral infection of both cell groups could be recognized as part of a strategy of immune evasion. In this sense, the specific immunity induced in HSV-infected individuals might be inferred to be a type of incomplete immunity.

4 | CONCLUSION

4.1 | Tactics for HSV vaccine development

In recent decades, different types of HSV vaccines, including inactivated vaccines, peptide vaccines containing various antigenic structures, and replication-deficient vaccines, have been investigated

for their efficacy and safety,[9] and these vaccines have been found to enable both cytotoxic T lymphocyte (CTL) responses in animals and neutralizing antibody production that blocked viral entry into cultured cells in classic neutralization assays.[20,146] However, a clinical trial of these vaccine candidates suggested that there were no clinical protective effects on human subjects, even though the immune response induced in rodent animal models was identified as being capable of protecting against viral attack.[9] This finding seems to suggest that the designed vaccine-induced immune response, which was mainly based upon the antigenic structure of viral surface glycoproteins, might not target various virus-encoded proteins that play roles in viral pathogenesis. Importantly, this characterized pathological process presents not only as vesicle lesions in epithelial and/or mucosal tissues but also as a modified phenotype of innate immune cells, including DCs and ILCs. The immune response elicited by HSV vaccine candidates based on viral glycoproteins cannot be restimulated by various antigenic molecules from virus-encoded proteins that are expressed transiently at different stages of infection, and antibodies and CTLs specific for viral surface proteins cannot control various pathological lesions triggered by the interactions of many viral molecules with cellular molecules in tissues. Furthermore, if the characterized pathogenesis of HSV infection is recognized as a systematic dynamic outcome of the interactions between virus-encoded molecules and cellular components, effective vaccine-induced immunity would comprise not only neutralizing antibodies specific for viral surface protein-binding receptors and/or specific CD8 cytotoxic T-cell subsets in local tissues but also an antibody profile capable of neutralizing various viral molecules that enable interactions with host cells and a specific CTL response against infected cells presenting various viral antigens. However, to achieve this type of vaccine-mediated immunity, the design for the HSV vaccine would be required to achieve the objectives presented below (Figure 3):

1. The vaccine candidate should have a viral replication cycle that mimics the HSV replication cycle but is substantially weaker and sufficiently long to ensure the activation of the local innate immune system and the subsequent activation of adaptive immunity.
2. The vaccine candidate should be capable of inducing the expression of the main viral molecules with pathological effects and exposing them to the host immune system.
3. The vaccine candidate should be designed to be readily taken up by antigen presenting cells, including DCs and/or ILCs and macrophages, without interference with antigen presentation processes or induction of cellular apoptosis events.
4. The vaccine candidate should efficiently remove viral molecules with serious pathological effects and be unable to lead to pathological lesions in host tissues.
5. Ideally, the vaccine candidate should itself possess no neurotropic infectivity, as described by Richards et al in a recent publication.[95] To satisfy these biological requirements in a vaccine candidate, a complex antigenic structure or an attenuated strain integrated with mutated structural genes could be generated with molecular techniques.

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CONFLICT OF INTEREST

The authors have no competing interests.

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