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REVIEW

$CD8^+$ T cells patrol HSV-1-infected trigeminal ganglia and prevent viral reactivation

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Abstract A hallmark of herpes viruses is their capacity to cause recurrent disease. Recurrences of herpes simplex virus (HSV)-1 disease do not result from reinfection from external sources, but rather from reactivation of virus that is maintained in a latent state in sensory neurons and periodically reactivates from latency to cause recurrent disease. Recent findings implicate HSV-specific $CD8^+$ T cells in immune surveillance of HSV-1 latently infected sensory neurons in trigeminal ganglia (TG) and inhibition of HSV-1 reactivation from latency. This review summarizes recent findings regarding the characteristics of the TG-resident $CD8^+$ T cell population and certain unique obstacles that might complicate the development of therapeutic vaccines.

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Herpes simplex virus (HSV) types 1 and 2 are enveloped, double-stranded DNA viruses. Though both viruses have the ability to infect a variety of epidermal and mucosal surfaces, HSV-1 most commonly infects oral facial regions, while HSV-2 typically infects the genital tract (Liesegang 2001). During lytic infection, HSV-1 sequentially expresses viral gene products necessary for successful replication of infectious virus. The virus uses the host RNA polymerase II to transcribe immediate early (IE or α) genes, some of which act as transcription factors for the expression of early (E or β) genes. Early gene translation signals DNA synthesis and thus sets the stage for late (L or γ) gene expression, which accounts for structural and capsid proteins. Some late genes, considered leaky late ($\gamma 1$), are moderately expressed before DNA synthesis with further amplification after DNA synthesis. True late ($\gamma 2$) gene expression occurs only after DNA synthesis (Knipe et al. 2007).

When introduced into the corneal epithelium, HSV-1 infects the termini of sensory neurons innervating the cornea. The virus then travels in a retrograde direction along the neuronal axons to the trigeminal ganglia (TG), where it replicates briefly in some neurons (Knipe et al. 2007). During this primary infection, HSV-1 replication in the TG is largely controlled by cells of the innate immune system including macrophages (through tumor necrosis factor and nitric oxide) and gamma delta T cell receptor (TCR) T cells (through interferon gamma (IFN-γ)) (Kodukula et al. 1999). By around 8 days after corneal infection in mice, HSV-1 enters a quiescent or latent state within all infected sensory neurons in the TG, and the

latent infection persists for the life of the host (Lekstrom-Himes et al. 2000).

HSV-1 latency can be defined as a quiescent state in which the viral genome is maintained as episomal DNA in neuronal nuclei for prolonged periods without production of infectious virions. Alternatively, HSV-1 latency can be defined in molecular terms as a state in which viral gene expression is largely repressed with the only abundant transcripts being latency-associated transcripts (LATs) that lack known translational products (Farrell et al. 1991). Several environmental and physiological stimuli including psychological stress, immune compromise, elevated levels of female sex hormones, and exposure to ultraviolet light are associated with HSV-1 reactivation from the latent state (Freeman et al. 2007; Liesegang 2001; Padgett et al. 1998). The term reactivation is defined in different ways by different investigators. Reactivation can be defined as the initiation of viral lytic gene expression following a period of latency. Alternatively, reactivation can be defined as the point at which infectious virions are produced following a period of latency. We prefer the latter definition because it is consistent with the clinical definition of reactivation, and it accommodates some viral lytic gene expression during latency as is seen with most other herpes viruses.

Virions that are produced following reentry of HSV-1 into the lytic cycle are usually transported in an anterograde direction to peripheral sites such as the lips or cornea, where they can cause recurrent diseases such as cold sores (lip lesions) or herpes keratitis (corneal lesions) (Knipe et al. 2007). A form of recurrent herpes keratitis called immune or stromal keratitis represents an HSV-1-induced immunopathological process in which severe corneal inflammation leads to progressive corneal scarring and visual compromise. Such disease affects 400,000 people in the USA with 50,000 new cases diagnosed each year (Institute 2010). In mice, most strains of HSV-1 travel from the TG to the brainstem without causing neurologic symptoms (Kastrukoff et al. 2010). With more neurovirulent strains or in immunocompromised mice, the virus can progress from the brainstem to the cerebral hemispheres causing potentially lethal encephalitis. In humans, HSV-1 is the leading cause of sporadic encephalitis with lesions occurring most frequently in the temporal lobe and less frequently in the brainstem (Gilden et al. 2007; Shoji et al. 2002).

The factors that influence HSV-1 entry into, maintenance of, and exit from latency remain poorly defined. Possible involvement of the host immune system in controlling HSV-1 latency was suggested by studies in mice where $CD8^+$ T cells were shown to infiltrate TG around the time that HSV-1 latency is established and position themselves in direct apposition to neurons (Liu et al. 2000). This initial population of $CD8^+$ effector T cells undergoes contraction giving rise to a stable memory effector population. During latency, the $CD8^+$ T cells remain in direct contact with neurons and express an activation phenotype, and many polarize their T cell receptor to the junction with neurons in an apparent immunologic synapse (Khanna et al. 2003). Since mice rarely if ever exhibit spontaneous HSV-1 reactivation from latency, the observed immunological synapse formation between $CD8^+$ T cells and neurons in mouse TG demonstrated that $CD8^+$ T cells can recognize latent virus, refuting the strongly held belief that HSV-1 can effectively hide from the host immune system during latency.

Human TG exhibit a similar localization of activated $CD8^+$ T cells to neurons that harbor HSV-1 in an apparently latent state (Theil et al. 2003; Verjans et al. 2007), suggesting that human $CD8^+$ T cells can also respond to latent virus. This is somewhat surprising in light of the ability of the HSV-1 immediate early gene product ICP47 to efficiently bind to the human transporters of antigen processing (TAPs) and block the transport of peptides into the ER for loading on MHC class I (Hill et al. 1995). This might be attributable to a change in the sequence of HSV-1 lytic gene expression during reactivation from latency (Tal-Singer et al. 1997), possibly resulting in a low level of ICP47 expression during reactivation. Moreover, the fact that $CD8^+$ T cells play an important role in controlling HSV-2 infection of the human genital tract (Zhu et al. 2007) suggests that ICP47 blockade of human TAPs is not absolute. We observed that HSV-specific $CD8^+$ T cells gain functional avidity (the ability to respond to low epitope densities) in the TG, but not in the lungs of latently infected mice, suggesting that the TG might exert a selective pressure for retention of high functional avidity $CD8^+$ T cells (Frank et al. 2010). Similar accumulation of high functional avidity $CD8^+$ T cells might render ganglion-resident human $CD8^+$ T cells less susceptible to the inhibitory effects of ICP47. However, one could also posit that the increased inhibitory effect of ICP47 on human compared to mouse TAPs might result in less efficient $CD8^+$ T cell control of HSV-1 latency, explaining in part the more frequent reactivation and shedding of virus in humans than in mice. Clearly, the mechanisms that control HSV-1 latency are more efficient in mice than in humans, making the mouse model of HSV-1 latency particularly effective for exploring these mechanisms.

Studies in C57BL/6 mice revealed that at least half of the TG-resident $CD8^+$ T cells are HSV specific and directed against a single immunodominant epitope on viral glycoprotein B ($gB_{498\text{-}505}$) (Khanna et al. 2003). Moreover, TG-resident $CD8^+$ T cells and specifically those recognizing the $gB_{498\text{-}505}$ epitope were shown to be capable of inhibiting HSV-1 reactivation from latency in ex vivo cultures of latently infected TG (Khanna et al. 2003; Liu et al. 2000). All of the $gB_{498\text{-}505}$-specific $CD8^+$ T cells present in

infected TG produced IFN-γ and released lytic granules when stimulated directly ex vivo, suggesting their potential use of these two effector mechanisms in preventing HSV-1 reactivation from latency (Frank et al. 2010; Khanna et al. 2003; Sheridan et al. 2009). Indeed, IFN-γ was shown to be one effector mechanism used by $CD8^+$ T cells to block HSV-1 reactivation from latency (Decman et al. 2005; Liu et al. 2000). IFN-γ blocked HSV-1 reactivation in ex vivo cultures of latently infected TG in part by inhibiting expression of ICP0, an HSV-1 gene product required for efficient viral reactivation from latency (Halford and Schaffer 2001), and in part by inhibiting a very late step in the viral life cycle subsequent to true late gene expression (Decman et al. 2005). However, IFN-γ was only able to block HSV-1 reactivation in about 50% of neurons that require $CD8^+$ T cell protection from reactivation in ex vivo TG cultures (Decman et al. 2005). In contrast, TG-resident $CD8^+$ T cells could completely block reactivation in these cultures, suggesting that $CD8^+$ T cells use other effector mechanisms in blocking HSV-1 reactivation from latency (Decman et al. 2005; Knickelbein et al. 2008).

The above findings lead to a search for an additional effector mechanism(s) used by $CD8^+$ T cells in preventing HSV-1 reactivation from latency. The lack of regenerative capacity of sensory neurons seemed to militate against the use of lytic granules to inhibit HSV-1 reactivation as the granzyme components of lytic granules inhibit virus replication through activation of the caspase system of infected cells leading to apoptotic death. Such an approach is acceptable in controlling infection of cells such as epithelial cells that can rapidly regenerate, but seemingly less acceptable in dealing with neurons. Moreover, studies in ex vivo cultures of latently infected TG provided indirect evidence that $CD8^+$ T cells blocked HSV-1 reactivation without killing neurons. Finally, both human and mouse neurons are surrounded by activated $CD8^+$ T cells, but never show signs of apoptosis (Knickelbein et al. 2008; Theil et al. 2003; Verjans et al. 2007). For these reasons, we favored a non-lytic protective mechanism by $CD8^+$ T cells.

Some TG-resident $CD8^+$ T cells produce tumor necrosis factor alpha (TNF-α) when stimulated directly ex vivo (Frank et al. 2010; St. Leger et al. 2011), but neutralization of TNF-α had no effect on HSV-1 reactivation in ex vivo TG cultures (our unpublished observation). Blocking Fas/Fas ligand interaction also failed to influence HSV-1 reactivation in TG cultures (our unpublished observations). Therefore, we were forced to consider the possible use of lytic granules in controlling HSV-1 latency. Indeed, patients with recurrent herpes keratitis tend to lose some sensation in their corneas over time (Gallar et al. 2010). However, it is unclear if this loss of sensation is due to neuronal death resulting from HSV-1 replication during a reactivation event or neuronal death due to $CD8^+$ T cell killing of neurons in combating reactivation. Interestingly, we demonstrated that $CD8^+$ T cells do use lytic granules to prevent HSV-1 reactivation from latency. Mice that are deficient in the lytic granule component perforin (forms pores in cell membranes through which the other lytic granule components pass) or granzyme B (cleaves cellular caspases leading to apoptosis) establish, but fail to maintain, HSV-1 latency in vivo, and perforin- and granzyme B-deficient HSV-specific $CD8^+$ T cells had reduced capacity to inhibit HSV-1 reactivation in ex vivo TG cultures (Knickelbein et al. 2008). However, a surprising observation was that protection is not mediated through the activation of neuronal caspases and apoptotic death. Instead, it appears that granzyme B contained in the lytic granules cleaves an important viral regulatory protein, infected cell protein 4 (ICP4) that is required for expression of viral β and γ genes (Godowski and Knipe 1986; Preston 1979; Watson and Clements 1980). This suggested a novel mechanism by which lytic granules could prevent viral replication without the need to kill the host cell. However, it did not explain why granzyme B activation of caspases was selectively blocked in latently infected neurons. A possible explanation derived from the observation that the LATs that are abundantly produced in latently infected neurons could inhibit caspase activation (Perng et al. 2000; Thompson and Sawtell 2001). Indeed, a recent study demonstrated that LATs can block granzyme B cleavage of caspases, suggesting that LATs act to prevent apoptosis of latently infected neurons during interactions with $CD8^+$ T cells (Jiang et al. 2011). Non-lytic use of lytic granules and IFN-γ by $CD8^+$ T cells might have advantages for both the host and the virus, limiting the frequency of recurrent herpetic disease while preserving the HSV-1 genome in the host neuron (Fig. 1). The observation that perforin-deficient HSV-specific $CD8^+$ T cells are more compromised than granzyme B-deficient cells in blocking HSV-1 reactivation (Knickelbein et al. 2008) suggests that other lytic granule components are involved as well.

An intriguing observation in C57BL/6 mice is that half of the TG-resident $CD8^+$ T cells are specific for a strongly immunodominant epitope on HSV glycoprotein B ($gB_{498\text{-}505}$) (Khanna et al. 2003). This 1:1 ratio of $gB_{498\text{-}505}$-specific $CD8^+$ T cells to $CD8^+$ T cells of unknown specificity was consistently maintained both within the effector population during acute infection and in the memory population during latency (Sheridan et al. 2009). Circumstantial evidence that all or most of the $CD8^+$ T cells in the infected TG were HSV specific came from studies demonstrating that only activated $CD8^+$ T cells enter the infected TG, that there is virtually no bystander activation of ovalbumin (OVA)-specific OT-1 $CD8^+$ T cells in draining lymph nodes

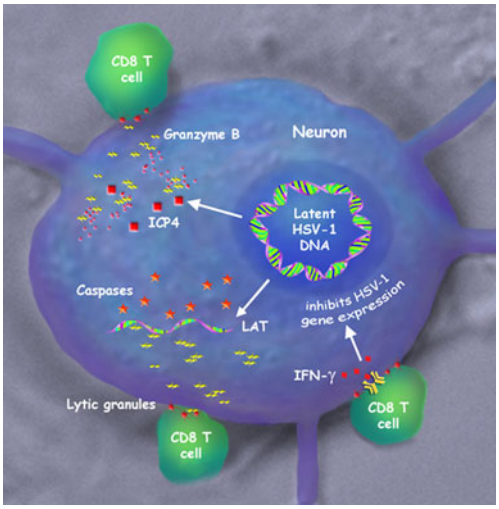

Fig. 1 CD8+ T cells control HSV-1 latency in trigeminal ganglia. In mice and humans, CD8+ T cells surround latently infected neurons in trigeminal ganglia. In C57BL/6 mice, these CD8+ T cells are all HSV specific with 50% recognizing an immunodominant epitope on HSV-1 glycoprotein B ($gB_{498\text{-}505}$) and the remaining 50% recognizing 19 subdominant epitopes on 11 HSV-1 proteins, most of which are expressed prior to viral DNA synthesis. In vivo, the $gB_{498\text{-}505}$-specific CD8+ T cells provide active immune surveillance as indicated by formation of immunological synapses and release of lytic granules at the junction with neurons. Directly ex vivo, these ganglion-resident $gB_{498\text{-}505}$-specific CD8+ T cells produce the antiviral cytokine IFN-γ and release lytic granules when stimulated with $gB_{498\text{-}505}$ peptide, and can use these two effector mechanisms to block HSV-1 reactivation from latency in cultures of latently infected TG. Interestingly, the lytic granule component granzyme B fails to activate the caspase system of the neuron presumably due at least in part to the accumulation of LATs in latently infected neurons that can block apoptosis by inhibiting caspase activation by granzyme B. Instead, granzyme B cleaves HSV-1 ICP4, an important regulatory protein required for viral early and late gene expression. Thus, CD8+ T cells can block HSV-1 reactivation from latency while sparing the infected neuron by producing IFN-γ and releasing lytic granules

following HSV-1 corneal infection, and that TG-resident $CD8^+$ T cells that are not specific for $gB_{498\text{-}505}$ can block HSV-1 reactivation from latency in ex vivo cultures of latently infected TG (Sheridan et al. 2009). These findings led to additional studies to identify the HSV-specific $CD8^+$ T cell repertoire in C57BL/6 mice. The HSV-1 proteome was scanned for peptide sequences predicted to bind with high affinity to H-2 K^b or H-2 D^b, the two MHC class I molecules expressed in C57BL/6 mice. The scan yielded 376 candidate peptides (St. Leger et al. 2011). $CD8^+$ T cells were screened for reactivity to the candidate peptides using intracellular IFN-γ as a readout following stimulation with peptide-pulsed targets. Based on the assumption that HSV-specific $CD8^+$ T cells would represent a small minority of cells in the secondary lymphoid organs of infected mice, we chose to use TG-resident $CD8^+$ T cells that appear to be highly enriched for HSV-specific cells for the initial screening of the peptides. This proved to be a good choice as the 376 peptides were quickly screened and 19 $CD8^+$ T cell epitopes were identified.

Of the 19 identified HSV-1 epitopes, one represented the immunodominant $gB_{498\text{-}505}$ epitope and another represented the previously identified ribonucleotide reductase 1 (RR1) epitope ($RR1_{822\text{-}829}$) (Salvucci et al. 1995). The remaining 17 peptides represented newly defined HSV-1 $CD8^+$ T cell epitopes. Several observations suggested that the 19 epitopes represent the entire HSV-specific $CD8^+$ T cell repertoire in C57BL/6 mice. The 19 peptides stimulated nearly all of the $CD8^+$ T cells in the TG; there was complete concordance in the epitopes that stimulated TG and splenic $CD8^+$ T cells, and in aggregate, the 19 peptides stimulated 19% of the $CD8^+$ T cells in the spleens of acutely infected mice, similar to the 17% that were stimulated by virus-infected targets (St. Leger et al. 2011). It was interesting to note that HSV-specific $CD8^+$ T cells selectively target a limited array of viral proteins. While the viral genome encodes at least 84 ORFs (Rajčáni et al. 2004), only 19 epitopes on 11 proteins were targeted by $CD8^+$ T cells. Moreover, nearly 80% of the epitopes are derived from viral proteins that are produced before viral DNA synthesis. Although the mechanism responsible for selective targeting of early genes is not known, the advantages to the host are obvious. Viral DNA can be infectious, and the HSV-1 genome copy number in latently infected sensory ganglia is directly correlated with reactivation frequency (Hoshino et al. 2007; Lekstrom-Himes et al. 1998). An additional interesting observation is that 73% of the HSV-specific response is directed towards nine peptides on three proteins, gB, RR1, and ICP8 (St. Leger et al. 2011), that are absolutely essential for the propagation of the virus in the host and thus least likely to mutate. We feel that this targeting elegantly displays the immune system's ability to choose targets having a high degree of conservation to eliminate the chance of escape variants that have the potential to compromise the host.

A possible explanation for the selective targeting of HSV-1 early genes might relate to the viral life cycle in the dendritic cells (DC) that are primarily responsible for the initial expansion of HSV-specific $CD8^+$ T cells (Smith et al. 2003). The life cycle of the virus is different in immature and mature DCs, causing a lytic infection (expression of all viral genes) in the former, but only an abortive infection (expression of α, β, and γ1 genes that are expressed before viral DNA synthesis) in the latter. Lytic infection leads to apoptosis of immature DCs in part through degradation of the FLICE inhibitory protein c-FLIP and in part due to reduced LAT expression in DC (Kather et al. 2010; Mikloska et al. 2001). Mature DCs retain HSV-1 entry receptors and can be infected by the virus, but survive abortive infection (Kruse et al. 2000) and can migrate from the infected tissue to play a crucial role in priming of HSV-CD8s during

mucosal infection (Lee et al. 2009). Therefore, we hypothesize that early in infection, mature DCs survive infection and preferentially present early and leaky late viral proteins that are expressed during abortive infection. Later, immature DCs that have undergone apoptosis will get phagocytosed by lymph node-resident DCs that can present viral antigen and prime additional virus-specific $CD8^+$ T cells (Smith et al. 2003). Infected DCs permitting only an abortive infection (Kruse et al. 2000) will preferentially prime $CD8^+$ T cells specific for early genes. Thus, the surviving directly infected DCs would preferentially present viral proteins that are produced before viral DNA synthesis.

Immunodominance is established among $CD8^+$ T cells responding to a variety of pathogens. However, the degree of dominance exhibited by $gB_{498\text{-}505}$-specific $CD8^+$ T cells far exceeds that observed in response to other pathogens (Freeman et al. 2010; Kotturi et al. 2007, 2008; Oseroff et al. 2008; St. Leger et al. 2011). Many factors can contribute to immunodominance including the efficiency of peptide generation by proteasomes (Chen et al. 2001), viral gene expression (Yewdell 2006), the peptide binding affinity for MHC (Kotturi et al. 2008), the epitope affinity for TCR (St. Leger et al. 2011), the frequency of epitope-specific $CD8^+$ T cell precursors (Kotturi et al. 2008), and the ability of epitope-specific $CD8^+$ T cell precursors to expand and survive. The strong immunodominance of the $gB_{498\text{-}505}$ epitope cannot be attributed solely to MHC or TCR affinity since all of the epitopes showed very high affinity for MHC and at least one showed similar TCR affinity (St. Leger et al. 2011). The RR1 protein is also expressed at high levels in infected cells (Salvucci et al. 1995). These findings suggested that the determining factor in the dominance of the $gB_{498\text{-}505}$ over the $RR1_{982\text{-}989}$ epitope is related either to the efficiency of peptide generation or to the characteristics of the epitope-specific $CD8^+$ T cell precursors (frequency, proliferative capacity, or survival characteristics).

The selective accumulation of HSV-specific $CD8^+$ T cells in the acutely infected TG appears to be due to selective activation of these cells in the draining lymph nodes. The evidence for this came from studies in which HSV-1-specific (gBTI.1) and OVA-specific (OT-1) $CD8^+$ T cells were transferred into $CD8^{-/-}$ mice followed by simultaneous HSV-1 corneal infection and immunization with OVA-pulsed DC. Both gBTI.1 and OT-1 $CD8^+$ T cells were expanded in the lymph nodes of these mice, and both cells accumulated in the TG. However, following contraction, the gBTI.1 cells maintained a stable memory population in the TG, whereas the OT-1 cells were gradually lost. Those experiments suggested that maintenance of a stable memory $CD8^+$ T cell population in the TG requires antigenic exposure (Sheridan et al. 2009). We know that $gB_{498\text{-}505}$-specific $CD8^+$ T cells are retained and maintain an activation phenotype during latency (Khanna et al. 2003) suggesting expression of HSV-1 glycoprotein B during latency. It will be interesting to determine if $CD8^+$ T cells that are reactive to subdominant epitopes on other viral proteins will also be retained during latency.

Future directions

Most HSV-1-induced pathology is associated with recurrent disease. The recent emergence of data establishing a role for TG-resident HSV-specific $CD8^+$ T cells in maintaining HSV-1 in a latent state in sensory neurons suggests that bolstering this population of cells through therapeutic vaccination might reduce the rate of recurrence of herpetic disease. Indeed, a recent study established that the absolute number of $CD8^+$ T cells within latently infected TG is inversely correlated with the frequency of reactivation from ex vivo ganglion cultures at a given latent viral load (Hoshino et al. 2007). The authors concluded that future HSV-1 vaccines should be evaluated based on their capacity to augment the TG-resident $CD8^+$ T cell population. Our laboratory demonstrated that exposure of mice to psychological stress inhibits the function of a large portion of the TG-resident $CD8^+$ T cells, resulting in HSV-1 reactivation from latency (Freeman et al. 2007). Moreover, Carbone and colleagues demonstrated that HSV-1 reactivation from latency is associated with a dramatic reduction in the TG-resident $CD8^+$ T cell population (Allan et al. 2006; Gebhardt et al. 2009). Thus, increasing the size of the TG-resident HSV-1-specific $CD8^+$ T cell population through therapeutic vaccination might prevent reactivation by maintaining a critical level of functional $CD8^+$ T cells following reactivation stimuli.

Unfortunately, a recent study identified a potential problem with the concept of bolstering the TG-resident $CD8^+$ T cell population through vaccination. Adoptive transfer of $gB_{498\text{-}505}$-specific effector or memory $CD8^+$ T cells into HSV-1 latently infected mice mimicked the effect of therapeutic vaccine. Although the transferred cells represented greater than 80% of the circulating $gB_{498\text{-}505}$-specific $CD8^+$ T cells through 4.5 weeks after transfer, none of the transferred cells found their way into latently infected TG (Himmelein et al. 2011). In fact, even when HSV-1 reactivation was induced and $CD8^+$ T cell numbers were dramatically reduced by exposure of latently infected mice to psychological stress and corticosterone, the $CD8^+$ T cell population recovered within the TG without infiltration of transferred cells. These findings suggest that once established, the TG-resident $CD8^+$ T cell population may not be accessible to circulating memory or effector or memory $CD8^+$ T cells that are generated in the periphery. In this way, the TG-resident $CD8^+$ T cell population resembles the tissue-resident memory cells that

were recently described as a compartmentalized memory population that is maintained in tissue with little or no replenishment from the peripheral blood (Wakim et al. 2010). Thus, devising ways to increase the accessibility of the latently infected TG to circulating HSV-specific $CD8^+$ T cells will be a significant challenge for future development of efficacious therapeutic vaccines targeted at preventing HSV-1 reactivation from latency and establishment of recurrent herpetic disease.

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