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Review:

Immune response of T cells during herpes simplex virus type 1 (HSV-1) infection*

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Abstract: Herpes simplex virus type 1 (HSV-1), a neurotropic member of the alphaherpes virus family, is among the most prevalent and successful human pathogens. HSV-1 can cause serious diseases at every stage of life including fatal disseminated disease in newborns, cold sores, eye disease, and fatal encephalitis in adults. HSV-1 infection can trigger rapid immune responses, and efficient inhibition and clearance of HSV-1 infection rely on both the innate and adaptive immune responses of the host. Multiple strategies have been used to restrict host innate immune responses by HSV-1 to facilitate its infection in host cells. The adaptive immunity of the host plays an important role in inhibiting HSV-1 infections. The activation and regulation of T cells are the important aspects of the adaptive immunity. They play a crucial role in host-mediated immunity and are important for clearing HSV-1. In this review, we examine the findings on T cell immune responses during HSV-1 infection, which hold promise in the design of new vaccine candidates for HSV-1.

Key words: Herpes simplex virus type 1; Adaptive immunity; T cells; Vaccine
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1 Introduction

Herpes simplex virus type 1 (HSV-1), from the alphaherpes virus subfamily, is an enveloped, nuclear-replicating, and large double-stranded DNA virus. The genome of HSV-1 is an about 152 kb linear double-stranded GC-rich DNA sequence, and contains two unique regions called the long unique region (U_L) and the short unique region (U_S) (Fig. 1a), which encodes at least 84 proteins (Kieff *et al.*, 1971). The genome of HSV-1 is located within the nucleocapsid, which is surrounded by a group of tegument proteins. The nucleocapsid and tegument proteins are surrounded by a lipid envelope studded with glycoproteins which are important for binding to and entry into new susceptible cells (Egan *et al.*, 2013). The major steps of the life cycle of HSV-1 are: entry into the host cell, viral gene expression, genome replication, virion assembly, and release of new infectious virus (Fig. 1b) (Kukhanova *et al.*, 2014). Three classes of genes of HSV-1 are expressed in a consecutive manner, including immediate early (IE) genes, early genes, and late genes. The products of IE genes regulate the expressions of early genes and late genes (Harkness *et al.*, 2014).

The primary infection of HSV-1 is mainly in epithelial or mucosal cells, and then establishes a latent infection when it is transported to the sensory ganglia (Nicoll *et al.*, 2012). During HSV-1 latent infection, the genome transcription is inhibited with the exception of a sequence encoding the latency-associated transcripts (LATs) (Wagner and Bloom, 1997; Preston, 2000; Efstathiou and Preston, 2005). The renewed lytic infection at epithelial or mucosal cells happens when there is reactivation of latent HSV-1 (Wuest and Carr, 2008).

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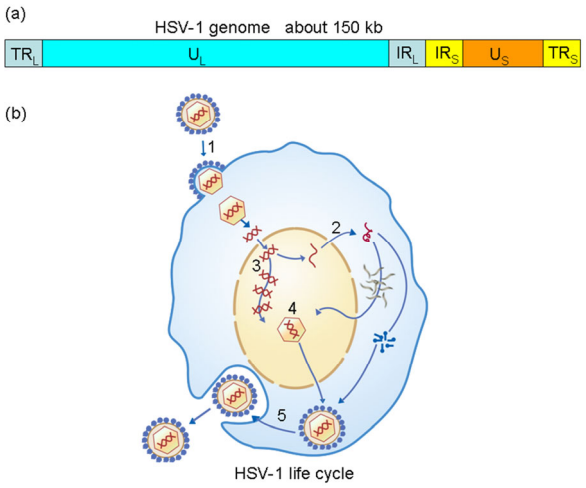

Fig. 1 Genome information and life cycle of HSV-1
(a) Structure of the HSV-1 DNA. The unique long (U_L) region is flanked by the terminal repeat (TR_L) and the internal repeat (IR_L). The unique short (U_S) region is bounded by the terminal repeat (TR_S) and the internal repeat (IR_S). (b) HSV-1 life cycle. 1: entry into the host cell; 2: viral gene expression; 3: genome replication; 4: virion assembly; 5: release of new infectious virus

HSV-1 infection is widespread, and its seropositivity may cover more than 70% of the world population. In developing countries, HSV-1 infection is universal, and acquired from intimate contact with family in early childhood (Whitley *et al.*, 1988). In developed countries, some data suggest that acquisition of HSV-1 is delayed from early childhood to young adulthood (Hashido *et al.*, 1999; Mertz *et al.*, 2003). In the United States, 65% of people have antibodies to HSV-1, which is similar to the epidemiology in Europe (Xu *et al.*, 2002). HSV-1 infection can cause clinical disease in various parts of the human body, such as genitalia, eye, oral, and central nervous system (CNS). The diseases associated with HSV-1 are listed in Table 1.

Inhibition of viral infection and clearance of the virus from infected cells rely on the innate and adaptive immunity of the host. The host innate immune system has evolved soluble components and specialized cells to block viral infection, replication, and shedding (Medzhitov and Janeway, 2000; Kawai and Akira, 2006). During viral infection, pattern recognition receptors (PRRs) have a role in detecting the viral pathogen-associated molecular patterns (PAMPs) in infected cells. The activated PRRs, such as Toll-like receptors (TLRs) and retinoic acid inducible gene-I (RIG-I)-like receptors (RLRs), will induce interferon production and cytokine release (Akira *et al.*, 2006). The cellular PRRs to detect HSV-1 PAMPs have been reviewed extensively (Paludan *et al.*, 2011; Melchjorsen, 2012). The type I interferon (IFN) signal pathway is the important first line of defense for the host against HSV-1. The innate immune cells including monocytes, neutrophils, dendritic cells (DCs), macrophages, and natural killer (NK) cells also play a crucial role in inhibiting HSV-1 infection (Kodukula *et al.*, 1999; Barr *et al.*, 2007; Murphy *et al.*, 2008; Zheng *et al.*, 2008; Mott *et al.*, 2011; 2014; Frank *et al.*, 2012; Kim *et al.*, 2012; Molesworth-Kenyon *et al.*, 2012; Swiecki *et al.*, 2013; Vogel *et al.*, 2014; Menasria *et al.*, 2015). During infection, HSV-1 has developed multiple mechanisms to evade innate host immune responses and attenuate host antiviral elements (Paladino and Mossman, 2009; Suazo *et al.*, 2015; Su *et al.*, 2016). Although the functions of host innate immunity such as type I IFN and innate immune cell activity are need to suppress HSV-1 replication and infection, the generation of both $CD8^+$ and $CD4^+$ T cells is ultimately required to inhibit viral infection, drive HSV-1 into latency, and repress reactivation. This review will summarize and discuss current findings of the T cell immune

Table 1 Diseases associated with HSV-1 infection

Infected body part	Disease	Reference
Skin	Cutaneous herpes	Zendri *et al.*, 2005; Faron *et al.*, 2016
	Genital herpes	Nieuwenhuis *et al.*, 2006; Khoury-Hanold *et al.*, 2016
Ocular	Herpes simplex keratitis (HSK)	Burrel *et al.*, 2013; Tsatsos *et al.*, 2016
	Uveitis	Krichevskaia *et al.*, 2005; van Velzen *et al.*, 2013
	Acute retinal necrosis	Mora *et al.*, 2009; Fong *et al.*, 2014
Orolabial	Cold sores	Richardson *et al.*, 2013; Chi *et al.*, 2015
	Oral ulcers	Sepulveda *et al.*, 2005; Nicolatou-Galitis *et al.*, 2006
CNS	Encephalitis	Bradshaw and Venkatesan, 2016; Eriksson *et al.*, 2016
	Meningitis	Eisenstein *et al.*, 2004; Azadfar *et al.*, 2014
	Alzheimer's disease	Beffert *et al.*, 1998; Itzhaki *et al.*, 1998

response during HSV-1 infection, which could facilitate the attempts of more effective vaccine development for treating HSV-1 infection.

2 Immune responses of $CD8^+$ T cells during HSV-1 infection

Among the immune cells involved in the immunity induced by pathogen invasion, $CD8^+$ T cells play a central role in host adaptive immunity against many intracellular pathogens and clearing the viruses from the host (Wiesel *et al.*, 2009; Kalia *et al.*, 2010). Following pathogen recognition in the context of major histocompatibility complex class I (MHC-I) on antigen presenting cells (APCs), the naive $CD8^+$ T cells could be differentiated into Tc1, Tc2, or Tc17 cells (Mosmann *et al.*, 1997; Lee *et al.*, 2011; Zhang and Bevan, 2011). During viral infection, the immune response of $CD8^+$ T cells was divided into three characteristic phases, which are the initial activation and expansion, a contraction phase, and the establishment and maintenance of memory (Kaech *et al.*, 2002a). During the acute phase of viral infection in humans, the robust immune responses of $CD8^+$ T cells have also been observed (Callan *et al.*, 1998). At the peak of proliferation, there is up to 10^4- to 10^5-fold expansion of $CD8^+$ T cells, which divide approximately every 6 to 8 h, and then undergo activation and differentiation after this dramatic proliferation (Murali-Krishna *et al.*, 1998). Upon antigenic stimulation, the expressions of granzymes and perforin are up-regulated by $CD8^+$ T cells, and then these cells become cytolytic and gain the ability to enter non-lymphoid tissues (Bachmann *et al.*, 1999; Cerwenka *et al.*, 1999; Kaech *et al.*, 2002a; 2002b; Wherry *et al.*, 2003). $CD8^+$ T cells also secret the IFN-γ when responding to viral infection, and IFN-γ promotes presentation of antigens to $CD8^+$ T cells through enhanced processing of viral peptides for loading into MHC-I, which promotes immune response and inhibits viral infection (Groettrup *et al.*, 1996; Schroder *et al.*, 2004).

Previous studies indicated that $CD8^+$ T cells might play a crucial role in restricting HSV-1 infection (Marrack and Kappler, 1987; Simmons, 1989). In line with the classic paradigm that HSV-1 infection is controlled by $CD8^+$ T cells, MHC-I-restricted $CD8^+$ T cells can be recovered from lymph nodes draining into herpetic lesions after HSV-1 infection on Day 4 (Nash *et al.*, 1980). $CD8^+$ T cells also have an ability to shut down HSV-1 infection in the trigeminal ganglia (TG) and prevent neurologic damage, and the response of $CD8^+$ T cells could be divided into acute and latent phases (Simmons and Tscharke, 1992; Liu *et al.*, 2000). In the mouse model, the infiltration peaks of $CD8^+$ T cells in mouse ganglia occurred on Day 12, and a great number of $CD8^+$ T cells persisted in the ganglia for up to 90 d. Using a murine flank scarification model, $CD8^+$ T cells were observed to be involved in inhibiting HSV-1 replication in the draining ganglia (Simmons *et al.*, 1992). In terms of effector molecules that are associated with $CD8^+$ T cells mediating immunity, alternatively it was reported that IFN-γ not only might exert an antiviral effect and block the replication of numerous viruses in vitro, but also has an antiviral activity in controlling HSV-1 infection in primary human neurons and astrocytes (Li *et al.*, 2011; 2012). Furthermore, another possible effector molecule is granzyme A (GrA), and the animals deficient in GrA show the decreased viral clearance from infection sites after peripheral HSV-1 inoculation (Pereira *et al.*, 2001).

The $CD8^+$ T cells might interact with many APCs during HSV-1 infection, such as DCs and ganglionic cells. The type and condition of APC used to characterize $CD8^+$ T cell responses are also critically important for the inhibition of HSV-1 infection. Compared with B cells, the fibroblasts are more susceptible to HSV-1-mediated down-regulation of human leukocyte antigen class I (HLA-I) and they were observed to poorly re-stimulate memory $CD8^+$ T cell responses (Yasukawa and Zarling, 1984; Kohl, 1991; Tigges *et al.*, 1996).

Tissue-resident memory T cells (T_{RM} cells) are a subtype of memory lymphocytes and reside in non-lymphoid tissues in humans and mice (Schenkel and Masopust, 2014). $CD8^+$ T_{RM} cells, a novel class of $CD8^+$ memory T cells, have been well characterized (Krzysiek *et al.*, 2013). During HSV-1 infection, virus-specific $CD8^+$ T_{RM} cells are created in both ganglia and mucosa (Khanna *et al.*, 2003; Gebhardt *et al.*, 2009; Ariotti *et al.*, 2014). $CD8^+$ T_{RM} cells exist in non-lymphoid tissue compartments for long periods, and now these cells are also found in brain, kidney, joints, and other non-barrier tissues, which

can trigger protective innate and adaptive immunity (Schenkel *et al.*, 2014). $CD8^+$ T_{RM} cells could express the effector molecules IFN-γ and granzyme B (GrB), and more these cells are not replenished from the circulating $CD8^+$ T cell pool (Mackay *et al.*, 2012). The roles of $CD8^+$ T_{RM} cells are listed in Fig. 2.

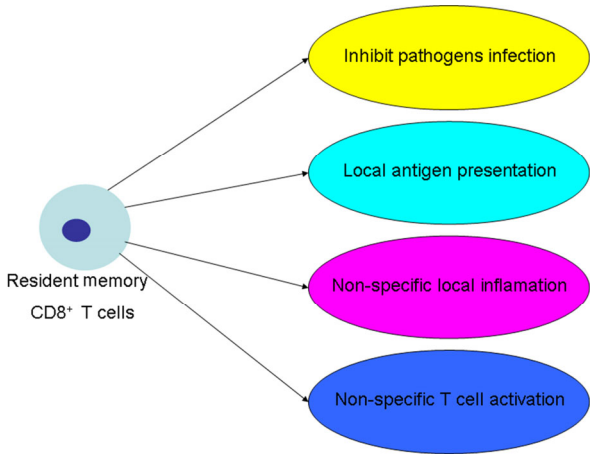

Fig. 2 Function of $CD8^+$ T_{RM} cells

3 Immune response of $CD4^+$ T cells during HSV-1 infection

In the host adaptive immune system, $CD4^+$ T cells are another important branch, which not only have the ability to regulate an effective immune response to pathogens, but also have a role in control of host survival. Naive $CD4^+$ T cells could differentiate into Th1, Th2, Th17, and induced regulatory T (iTreg) cells through interaction with antigen-MHC complex, and $CD4^+$ T cell differentiation depends on the cytokines of the microenvironment (Luckheeram *et al.*, 2012; Zheng, 2013). $CD4^+$ T cells have ability to restrict and eliminate acute viral infection, and depend on the distinct phenotypes with their respective cytokine profiles. $CD4^+$ T cells also modulate the functions of adaptive immunity and the innate immune cells (Sant and McMichael, 2012). Th1 cells have been regarded as critical for immunity to intracellular microorganisms and Th2 cells for immunity to many extracellular pathogens, including helminthes (Mosmann and Coffman, 1989; Paul and Seder, 1994). Treg cells function is needed to limit the extent of virus-induced inflammatory lesions, which implies that expanding and activating Tregs could be therapeutically valuable (Sehrawat and Rouse, 2011). During HSV-1 infection, the expression of IL-17 was up-regulated mainly through the Th17 cells in host cornea. Th1 cells are also responsible for orchestrating herpes stromal keratitis (HSK) during viral infection (Suryawanshi *et al.*, 2011).

In the HSV-1 corneal infection model, HSV-1 replication is largely eliminated by 4–6 day post infection (dpi), and the $CD4^+$ T cells that mediate HSK infiltrate the cornea around 7 dpi (Lepisto *et al.*, 2006; Yun *et al.*, 2014). Previous study has shown that the $CD4^+$ T cells are important for preventing genital disease in a mice model during HSV-1 infection (Kuklin *et al.*, 1998). When the mice are inoculated intravaginally (i.vag.) with HSV-1, $CD4^+$ T cells can accumulate and persist within the spinal cords and dorsal root ganglia, which suggested that $CD4^+$ T cells have the ability to clear virus from both neural and genital sites after HSV-1 primary infection (Johnson *et al.*, 2008). It had been demonstrated that the $CD4^+CD25^+$ Tregs participate in T cell immune response to HSV-1 (Suvas *et al.*, 2003). Following i.vag. inoculation of HSV-1, the number of $CD4^+$ T cells from iliac lymph nodes, spinal cords, or dorsal root ganglia generally peaked around 6 or 8 dpi, and these cells increased expression of the activation marker CD25, CD44, or CD69 (Johnson *et al.*, 2008). $CD4^+$ T cells are expanded in the draining lymph nodes (DLNs) and re-stimulated in the infected cornea to regulate the destructive inflammatory disease after HSV-1 corneal infection (Buela and Hendricks, 2015). Recruitment of memory $CD4^+$ T cells after infection of HSV-1 is also involved in the development of Th1 cells (Sin *et al.*, 2000). DCs are resident in the DLNs and account for the expanding of naive HSV-specific $CD4^+$ T cells in DLNs and the re-stimulating of the $CD4^+$ T effector cells that infiltrate the cornea to mediate HSK (Hendricks *et al.*, 1992). $CD4^+$ T cells contribute to protection against HSV-1 in mice and ablation of $CD4^+$ T cells increased susceptibility in naive animals (Manickan *et al.*, 1995a; 1995b). In the mice model, $CD4^+$ T cells are sufficient and have a ability to inhibit and clear HSV-1 from both neural and genital sites after primary infection (Johnson *et al.*, 2008).

4 Infiltration of $CD8^+$ and $CD4^+$ T cells into central nervous system during HSV-1 infection

Despite the fact that the CNS of a host generally has the restrictive nature of the blood-brain barrier (BBB), $CD8^+$ and $CD4^+$ T cells can infiltrate into CNS during a variety of disease states and viral infection (Stohlman *et al.*, 1998; Marten *et al.*, 2003). When animals are exposed to glucocorticoids, the CNSs of them are shown to be vulnerable, which could enhance the susceptibility to viral infection. In the mouse model, psychological stress can induce the production of glucocorticoid, which enhances the infection of HSV-1 in mice and causes the development of HSV-1 encephalitis (HSE) (Nair *et al.*, 2007). In a mouse model of HSE, the HSV-1-specific T cells infiltrated into CNS, and the brain of the mouse had an increase in $CD8^+$ and $CD4^+$ T cells during HSV-1 infection (Anglen *et al.*, 2003). Multifocal brain demyelination (MBD) has been reported in susceptible mouse strains upon lip inoculation with HSV-1 and immunosuppression prevents the development of such lesions (Kastrukoff *et al.*, 1987; 1993). $CD8^+$ T cells appear to be involved in the focal lesions of the brain and the depletion of such cells prevents lesion development (Hudson and Streilein, 1994). Due to the limited evidence, it still remains unclear whether $CD8^+$ T cells are responsible for limitation of HSV-1 replication and spreading within the CNS prior to an infection, or the delayed entrance of $CD8^+$ T cells could result in pathology (Anglen *et al.*, 2003).

The microglia, mstrocytes, perivascular macrophages, DCs, and endothelial cells of the brain have a function in presenting antigen to T cells in CNS (Aloisi, 1999; 2001; Aloisi *et al.*, 2000). During HSV-1 infection, the dendritic-like cells and macrophage-like cells increase the expression of $H\text{-}2K^b$, which indicates a potential role of these cells to prime of HSV-1-specific $CD8^+$ T cells in host CNS (Nair *et al.*, 2007).

5 Exhaustion of $CD8^+$ T cells during HSV-1 infection

The $CD8^+$ T cells can be exhausted during chronic viral infection. These exhausted $CD8^+$ T cells exhibit lost memory potential and poor effector function (Zajac *et al.*, 1998; Wherry, 2011; Schietinger and Greenberg, 2014). The first report on $CD8^+$ T cells exhaustion was found in mice when infected with lymphocytic choriomeningitis virus (LCMV), and virus-specific $CD8^+$ T cells become less functional, as the infection persists, and may gradually lose their effector function, including proliferation, cytotoxicity, and cytokine production (Zajac *et al.*, 1998). In addition, the exhaustion of $CD8^+$ T cell function has been demonstrated in several human chronic virus infections, including hepatitis C virus (HCV), hepatitis B virus (HBV), and human immunodeficiency virus (HIV). The inhibitory receptors are expressed in exhausted $CD8^+$ T cells, such as programmed cell death protein 1 (PD-1), T-cell immunoglobulin domain and mucin domain-3 (Tim-3), cluster of differentiation 244 (CD244), B- and T-lymphocyte attenuator (BTLA), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), CD160, and killer cell lectin-like receptor subfamily G member 1 (KLRG1) (Bengsch *et al.*, 2010; Wherry, 2011).

HSV-1 can reactivate from the TG, where there is a sizable pool of virus-specific $CD8^+$ T cells. This phenomenon may depend on exhausting $CD8^+$ T cells (Hoshino *et al.*, 2007; Chentoufi *et al.*, 2010). PD-1 is the most common inhibitory marker expressed in exhausted $CD8^+$ T cells (Barber *et al.*, 2006; Petrovas *et al.*, 2007; Fourcade *et al.*, 2010; Sakuishi *et al.*, 2010). Besides the expression of PD-1, the high expressions of Tim-3 and CTLA-4 were also detected on the HSV-1-specific $CD8^+$ T cells from LAT^+ TG, which helped to discriminate between exhaustion and activation (Srivastava *et al.*, 2016). During HSV-1 latency infection, LAT influences the $CD8^+$ T cell levels and exhaustion. LAT^+ HSV-1 can present more viral agent to $CD8^+$ T cells, and this leads to increase in the expression of PD-1/Tim-3 and $CD8^+$ T cell exhaustion. There are three subsets of exhausted $CD8^+$ T cells in the TG of mice latently infected by HSV-1, the first one expressing PD-1, the second expressing Tim-3, and the third expressing both PD-1 and Tim-3 (Allen *et al.*, 2011). The GrB of $CD8^+$ T cells plays a major role in cytotoxic lytic granule-mediated apoptosis of cells. HSV-1 LAT not only restricts the GrB-induced cell apoptosis, but also inhibits the GrB-induced cleavage of caspase-3 (Jiang *et al.*, 2011).

6 Vaccine for HSV-1

HSV-1 has the ability to build a primary and latent infection in human bodies, and causes serious diseases in human beings (Laing *et al.*, 2012). It will benefit public health worldwide by reducing HSV-1 infection in human beings, and the efficient and effective pathway to control viral infectious disease is to inject vaccines. However, many of people are infected by HSV-1 during childhood, and the most of infected persons never undergo recurrent herpetic disease (Khanna *et al.*, 2004). Therefore, the efficient and effective approach to prevent the infection of HSV-1 is prophylactic vaccination. The method to produce a therapeutic vaccine is targeting the viral proteins during HSV-1 latent infection, which proves more efficacious in restricting recurrent disease in human beings.

The advantages and disadvantages of experimental vaccine formats, which are mixture of viral proteins, peptides, attenuated replication-competent viruses, and replication-defective viruses, are reviewed (Stanberry *et al.*, 2000). Many vaccine types including prophylactic and therapeutic containing viral DNA, glycoproteins, or replication-defective virus have been built in the past ten years. Nowadays, the approaches to develop vaccines are focused on the mechanism of viral evasion of the host immune system, and combination with the use of new and more specific adjuvants (Coleman and Shukla, 2013).

Researchers are interested in exploiting T cells to develop the vaccines, because the T cells of the host have specific and long-term immunologic memory and the ability to clear the virus in vitro and in animals (Laing *et al*., 2012). It is known that T cells have taken part in protective immunity after vaccination and correlate with viral reactivation in animal manipulation (Noisakran and Carr, 1999; Liu *et al.*, 2000; Sheridan *et al.*, 2009). Some studies suggest that T cell epitope specificities vary with different clinical presentations of HSV-1, and the epitope discovery has facilitated investigation of HSV-1-specific T cells in the search for a natural immune response (Chentoufi *et al.*, 2008). T cells respond to a complex and serious pathogen with HSV-1, which has been decoded with a linked set of cellular and molecular tools to reveal novel candidate vaccine antigens (Jing *et al.*, 2012). During HSV-1 cornea infection in mouse models, it has been shown that the $CD8^+$ T cells might have no influence on the immunopathology in HSV-1. However, $CD8^+$ T cells are protective at peripheral sites of infection and in the TG of the host, so a vaccine targeting $CD8^+$ T cells might be particularly efficient and effective (Khanna *et al.*, 2004).

Based on the protective immune response of T cells, it is important to develop a vaccine that elevates T cells. The best protection of the host during viral infection is to induce stronger cell-mediated immunity as well as better humoral responses, because viruses have used clever immune evasion strategies to inhibit the neutralizing antibody response (Coleman and Shukla, 2013). Nowadays, there has no specific vaccine or immunization strategy for HSV-1, but fascinating recent work comparing HSV-1-seropositive persons with and without histories of symptomatic orolabial herpes raises the possibility that humoral response patterns to specific proteins, or T-cell response patterns to defined epitopes within HSV-1 glycoproteins, may correlate with clinical severity, offering a set of criteria for rational down-selection of vaccine candidates (Chentoufi *et al.*, 2008; Dasgupta *et al.*, 2012).

7 Conclusions

In summary, HSV-1 is one of the persistent pathogens of human beings, and can cause a variety of diseases, such as cold sores, cutaneous herpes, genital herpes, and encephalitis. HSV-1 can establish a latent infection in TG of host, while $CD4^+$ and $CD8^+$ T cells can control the reactivation of the HSV-1 by surrounding latently infected neurons. The interactions between the host immunity and HSV-1 are very complicated. There is a battle between the host and HSV-1, and construction of a potent HSV-1-specific T cell immunity relies on multifaceted DCs priming of T cells as well as both $CD4^+$ and $CD8^+$ T cell cooperation at several stages and anatomic sites. Thus, favored vaccines elicit complex T cell responses, and likely also B cell responses, to generate long-lasting virus-neutralizing antibodies. Now the approaches to design the new vaccine against HSV-1 are by attracting and retaining T_{RM} cells in peripheral tissue locations. In any case, development of a useful HSV-1 vaccine needs to overcome the challenges posed by HSV-1 to traditional vaccine strategies.

Compliance with ethics guidelines

Jie ZHANG, Huan LIU, and Bin WEI declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：一型单纯疱疹病毒感染与 T 淋巴细胞免疫反应

概　要：文章概述了一型单纯疱疹病毒基因组的组成和在宿主细胞的生活周期，以及感染时引起的与人类相关的疾病；阐述了一型单纯疱疹病毒感染时引起的 CD4 和 CD8 阳性 T 淋巴细胞的免疫反应；以及 CD8 阳性 T 淋巴细胞的功能耗竭；简要探讨了一型单纯疱疹病毒的疫苗研发的相关策略和前景；方便读者理解 HSV-1 感染和 T 淋巴细胞免疫的关系。

关键词：一型单纯疱疹病毒；适应性免疫；T 淋巴细胞；疫苗

Introducing editorial board member:

Dr. Bin WEI, the author of this invited review, is an editorial board member of *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)*. He did postdoctoral research at the University of Cambridge and University of Oxford from 2002 to 2009. His main research interests include: (1) design and development of new therapeutic and preventive vaccines; (2) the mechanisms of respiratory inflammation, nerve system inflammation, and tumor-associated inflammation caused by viral infection; (3) the mechanisms of signal transduction mediated by viral invasion receptors and lymphocyte function receptors on viral inflammatory response.