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Review

The challenges and opportunities for the development of a T-cell epitope-based herpes simplex vaccine

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ABSTRACT

Herpes simplex virus type 1 and type 2 (HSV-1 & HSV-2) infections have been prevalent since the ancient Greek times. To this day, they still affect a staggering number of over a billion individuals worldwide. HSV-1 infections are predominant than HSV-2 infections and cause potentially blinding ocular herpes, oro-facial herpes and encephalitis. HSV-2 infections cause painful genital herpes, encephalitis, and death in newborns. While prophylactic and therapeutic HSV vaccines remain urgently needed for centuries, their development has been difficult. During the most recent National Institute of Health (NIH) workshop titled "*Next Generation Herpes Simplex Virus Vaccines: The Challenges and Opportunities*", basic researchers, funding agencies, and pharmaceutical representatives gathered: (*i*) to assess the status of herpes vaccine research; and (*ii*) to identify the gaps and propose alternative approaches in developing a safe and efficient herpes vaccine. One "common denominator" among previously failed clinical herpes vaccine trials is that they either used a whole virus or a whole viral protein, which contain both "pathogenic symptomatic" and "protective asymptomatic" antigens and epitopes. In this report, we continue to advocate developing "asymptomatic" epitope-based sub-unit vaccine strategies that selectively incorporate "protective asymptomatic" epitopes which: (*i*) are exclusively recognized by effector memory $CD4^+$ and $CD8^+$ T cells (T_{EM} cells) from "naturally" protected seropositive asymptomatic individuals; and (*ii*) protect human leukocyte antigen (HLA) transgenic animal models of ocular and genital herpes. We review the role of animal models in herpes vaccine development and discuss their current status, challenges, and prospects.

1. Introduction

In the current era of effective drug therapies, many of the maladies that struck down our ancestors have been eliminated. However, diseases caused by herpes simplex virus type 1 and type 2 (HSV-1 & HSV-2) infections, which have been prevalent since the ancient Greek times, still affect a staggering number of the world's population to this day [1]. Over a half billion individuals, between fourteen and forty-nine years, around the world are clinically affected by HSV-2 [1]. The sub-Saharan African populations are most dramatically afflicted, with up to 50% of women and 40% of men in some regions suffering from genital herpes (NHANES-2005–2010). HSV-1 & HSV-2 infections cause a wide range of diseases throughout human life [1–9] (Fig. 1). Globally, HSV-1 is much more prevalent than HSV-2 (CDC), causing significant morbidity especially among young adults in western societies, where up to 63% are sero-positive. Genital herpes is one of the most common sexually transmitted infections, with a higher prevalence in women than men. Recent immuno-epidemiological evidence suggest that: (*i*) there is an increasing proportion of genital herpes cases associated with HSV-1 and (*ii*) the majority of infected individuals exhibit frequent and brief shedding episodes that are most often asymptomatic [10] and Fig. 2A. This non-apparent asymptomatic shedding likely contributes to high HSV transmission rates [10]. In the United States, there are 500,000 cases/year of oral herpes caused by HSV-1, 300,000 cases/year of genital herpes caused by HSV-1 and/or HSV-2, 20,000 cases/year of ocular herpes caused

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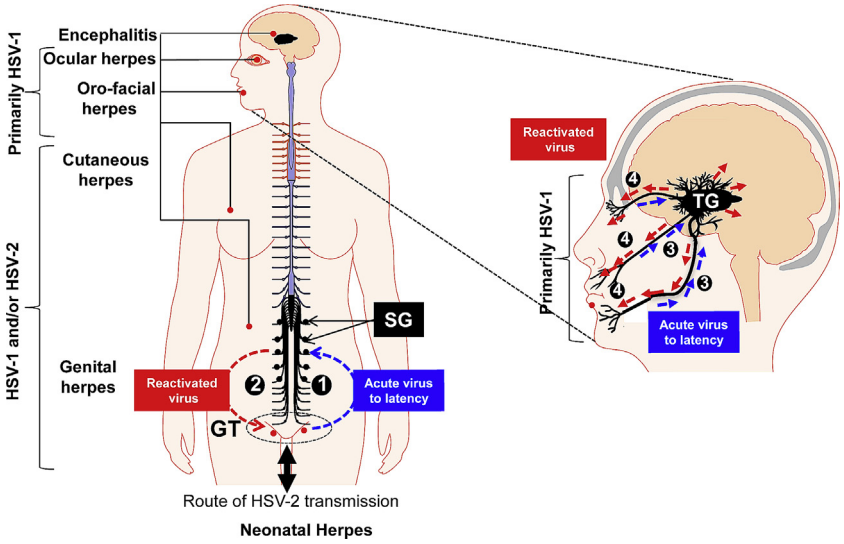

Fig. 1. The natural history of genital (*left*) and oro-facial (*right*) herpes infection. HSV-1 and HSV-2 are transmitted by close interpersonal contact (such as during intravaginal/oral sex, during birth or eye contact), and preferentially infects muco-cutaneous epithelium around the genital tract (GT), around the lips (cold sores), nose and eyes. *Right*: While most of genital herpes is caused by HSV-2 reports of HSV-1 genital infection are increasing. HSV-2 infections is a major public health problem. (1) The virus replicates in the TG and then travels along nerves to the sacral ganglia (SG) that control the GT, where it establishes a latent infection. (2) Recurrent genital herpes is the most prevalent sexually transmitted disease. *Left*: (1) Ocular herpes is mainly caused by HSV-1, which infects the cornea and then establishes latency in sensory neurons of the trigeminal ganglia (TG). (2) Sporadic spontaneous reactivation of HSV-1 from latently infected neurons leads to viral shedding in saliva and tears which can cause symptomatic recurrent Herpes Stromal Keratitis (HSK), a blinding corneal disease.

by HSV-1, and 1500 cases/year of herpes encephalitis [11,12]. HSV-2, but not HSV-1, appears to be linked with a two- to three-fold increase of risk of HIV-1 acquisition [1]. In addition to causing painful blisters, HSV-2 can cause encephalitis and death in newborns from vertical transmission [1].

The development of antiviral medications has had little discernible impact on herpes epidemiology [13,14]. Meanwhile, the development of effective vaccines against herpes viruses has been notoriously difficult, largely because HSV-1 & HSV-2 have complex life cycles, and the majority of infections remain clinically dormant and silent (i.e. latent) in the body for long periods of time (Fig. 1). Of note, it is surprising that only one vaccine strategy (i.e. vaccination with glycoproteins B and D (gB and gD)) has been tested during the last 18 years in human trials to prevent genital herpes [15–17]. No other vaccine strategy and vaccine trial against ocular or oro-facial herpes have succeed to reach phase I or phase II for over a decade and a half now. This by itself attests to the scientific and logistical difficulties facing HSV vaccine development. The latest failures of clinical herpes vaccine involving the employment of HSV-2 gD have brought on additional challenges in securing financial support from funding agencies and pharmaceutical companies for vaccine development and clinical trials [15–17].

The development of subunit herpes vaccines has been focused during the last two decades on HSV envelope glycoproteins gB and gD. However, studies from both mice [18–22] and humans [23–26], have showed nonstructural tegument proteins are major targets of HSV-specific $CD4^+$ and $CD8^+$ T cells, making them excellent candidates to be incorporated in future herpes vaccine candidates. In HSV-1 infected B6 mice, it appears that the vast majority of $CD8^+$ T cells are specific to β and γ1 proteins that are expressed before viral DNA synthesis with the ribonucleotide reductase 1 and 2 (RR1 and RR2) being major nonstructural targets [22]. Among the nonstructural proteins that are major targets of humans HSV-specific $CD4^+$ and $CD8^+$ T cells are the immediate early protein, ICP0 [26], the tegument proteins UL21, UL25, UL39, UL46, UL47 and UL49, and the capsid protein UL6 [23–25,27–30]. We strongly believe that the appropriate response to the recent "failure" of clinical HSV vaccine trials using HSV-2 gB and gD proteins is to identify other immediate early and tegument target antigens and to intensify our efforts in order to understand the mechanisms of humoral and cellular protective immunity in humans. In doing so, we may proceed to pre-clinically test novel vaccine approaches, discovered in vitro in humans, in reliable "humanized" animal models, such as HLA transgenic mice, rabbits and guinea pigs.

A "common denominator" among previously failed clinical herpes vaccine trials is that they used either a whole virus or whole glycoproteins, which contain both protective "asymptomatic" antigens/epitopes and pathogenic "symptomatic" antigens/epitopes (Fig. 2 and Fig. 3). We therefore continue to advocate our "asymptomatic" herpes vaccine approach (reviewed in [9]). This new approach is based on determining the immune mechanisms by which seropositive asymptomatic individuals are "naturally" protected from recurrent herpes disease throughout their lives. We believe that instrumental components for the development of an effective HSV vaccine include both the characterization of the phenotype and function of the T cell-based immune responses in the genital tract mucosa lining that prevents HSV-2 acquisition and development of an improved mucosal vaccine approach to boost effector memory T cell responses [1,31].

In the most recent workshop on "*Next Generation Herpes Simplex Virus Vaccines: The Challenges and Opportunities*" convened by the National Institute of Allergy and Infectious Diseases (NIAID) in Washington, DC, (October 22–23rd 2012), the future of the HSV vaccine was discussed among basic researchers, clinicians, funding agencies, and pharmaceutical representatives [11,12] (see the list of participants in Appendix A). The objectives were: (*i*) to assess the current status of herpes vaccine research, (*ii*) to identify the gaps in our knowledge, and (*iii*) to propose our best approaches in developing the next generation of herpes vaccines.

Although much remains unknown about the protective immune effector of ocular, genital, and oro-facial herpes (Figs. 1 and 2), improved knowledge of HSV immuno-epidemiology, pathogenesis, and host immunity should help guide new vaccine strategies for disease prevention and control.