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HSV-2 vaccine: Current state and insights into development of a vaccine that targets genital mucosal protection

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ABSTRACT

HSV-2 is one of the most prevalent sexually transmitted infections that result in significant morbidity and financial burden on health systems around the world. Recurrent and asymptomatic re-activation accompanied by viral shedding is common among sero-positive individuals, leading to relatively high efficiency of transmission. Prophylactic HSV-2 vaccines are the best and cheapest option to address the problems associated with HSV-2 infections globally. However, despite persistent efforts, the search for an efficacious vaccine for HSV-2 remains elusive. In this review, the current state of HSV-2 vaccines and the outcome of past human trials are examined. Furthermore, we discuss the evidence and strategies from experimental mouse models that have been successful in inducing protective immunity in the genital tract against HSV-2, following immunization. Future vaccination strategies that focus on induction of robust mucosal immunity in the genital tract may hold the key for a successful vaccine against HSV-2.
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1. Introduction

Herpes simplex virus type 2 (HSV-2) is a sexually transmitted virus that is the major cause of genital herpes, a highly prevalent infection among sexually active people worldwide. HSV-2 infects more than 500 million people worldwide and causes an estimated 23 million new infections each year [1]. CDC estimates from 2005 to 2008 show that 16% of the population between the ages of 14–49 in United States is seropositive for HSV-2 and 58% is seropositive for HSV-1, which is emerging as a major cause of genital herpes infections [2]. Globally, prevalence rates of HSV-2 are highest in Sub-Saharan Africa where greater than 80% of the population is seropositive for HSV-2 [3]. Seroprevalence in women is up to twice as high as men, and increases with age [2].

Despite the recognition that HSV-2 infection has high rates of transmission and is widely prevalent in the general population, the economic impact of genital herpes, even in developed regions like North America, is not clearly understood. Based on an estimated 3.1 million symptomatic episodes per year in the United States, the annual direct medical cost due to genital herpes in 1996 was determined to be between $283 and $984 million USD [4]. Other studies estimated the direct medical cost of genital herpes at $166 million for the years 1992–1994 and $207 million for 1999 [5]. Mathematical modeling predicts the 25 year costs attributable to HSV-2 infection in a 1000 couple cohort at $175,000 to $495,000, with a predicted cost effectiveness ratio of $8200 per infection averted [6].

2. HSV pathogenesis

A high proportion of genital herpes infections can go unrecognized by both patients and clinicians because clinical signs and symptoms can be quite mild or atypical and need to be confirmed serologically. Majority of both men and women with a first episode of clinically apparent genital HSV-2 disease have localized symptoms, such as pain at the site of the lesion and regional swollen lymph nodes [7]. Pathology associated with HSV is mainly caused by a direct cytopathic effect of the virus, resulting in cellular lysis and focal necrosis of the infected area. In its clinical presentation, primary infection begins with macules and papules and progresses to vesicles, pustules, and mucocutaneous lesions. HSV infects epithelial cells at skin and mucosal surfaces during primary infection, then travels via retrograde transport along nerve axons to the

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dorsal root ganglia (DRG), where latency is established [8]. While epithelial cells are destroyed during lytic HSV replication, neuronal cells are not destroyed and provide a reservoir for latent virus. HSV reactivations from latency in sensory nerve ganglia occur periodically and leads to neuronal anterograde transport of virions to mucocutaneous regions, where productive replication causes recurrent clinical manifestations such as ulceration [7]. Viral reactivation may be asymptomatic or may be associated with prodrome (tingling or burning) or a classic genital ulcer. Reactivation can be caused by numerous factors, including stress, hormonal changes and immunosuppresion.

Transmission of HSV from mother to infant during birth is the most serious complication of genital herpes, and women who acquire HSV during pregnancy are at the highest risk of transmitting the infection [9]. Neonatal herpes can result in long-term neurologic sequelae, blindness or mortality [10]. The estimated incidence of neonatal herpes varies widely, from 4 to 31 in 100,000 live births [11,12]. Furthermore, a recent meta-analysis concluded HSV-2 infection to be associated with a threefold increase in susceptibility to HIV-1 in both men and women from the general population [13]. Part of this increased susceptibility may be attributed to HSV-2-induced ulcerations, which create a breach in the physical barrier of the genital epithelium [14]. Genital HIV-1 shedding is also markedly increased during clinical HSV-2 reactivations, accompanied by an increase in HIV-1 plasma viral load [15]. Herpetic lesions and possibly asymptomatic HSV-2 mucosal shedding generates an influx of activated $CD4^+$ T cells that persist for months after healing, which may facilitate acquisition of HIV [16]. In addition to the direct effect on HIV-1 infection, HSV-2 infections can also enhance HIV-1 replication via indirect effects, including induction of a pro-inflammatory microenvironment in the genital tract that drives HIV-1 long terminal repeat (LTR) activation [17].

3. Viral shedding and transmission dynamics

Since most primary HSV-2 infections are subclinical, majority of infected people are unaware that they have been exposed to HSV-2 [18]. Subclinical viral shedding accounts for the majority of transmitted HSV-2 [19]. This is because asymptomatic shedding occurs much more frequently than symptomatic reactivation of the disease. More recent studies using intensive sampling (every 6 h) of the genital and oral mucosa have demonstrated that most HSV detection episodes are short (median 13 h), subclinical, and rapidly cleared [20] which corroborates data obtained from mathematical modeling [21]. Furthermore, in studies where HSV-2 infected persons collected daily genital swabs, HSV was detected on a median of 12%–28% of days [22] and was found on 10% of days even among persons with asymptomatic HSV-2 infection [23]. Studies in HSV-2 serodiscordant couples have shown that most HSV-2 transmissions occur during periods of subclinical shedding in the source partner [24] and that transmission occurs relatively efficiently with a median number of 40 sexual acts prior to HSV-2 acquisition [25]. In contrast, others have identified HSV-2 seronegative persons in long-term HSV-2–discordant sexual relationships [26].

4. The immune response to HSV-2

The natural immune response that follows a genital infection in humans requires both the innate and adaptive immune system to clear the infection. Viral products can be sensed by a number of innate immune and non-immune cells via pattern recognition receptors, such as Toll-like receptors (TLRs), which recognize highly conserved pathogen-associated molecular patterns, such as viral DNA and RNA. Single nucleotide polymorphisms in human TLR2 [27] and TLR3 [28] have been associated with susceptibility to increased HSV-2 disease and childhood fatality, respectively, indicating the importance of invariant innate recognition pathways in HSV protection in humans. TLR activation in response to viral recognition typically results in the production of type I interferon (IFN), which includes IFN-α and IFN-β [29]. These molecules usually act on surrounding cells, via their cognate receptors, to initiate an antiviral state whereby antiviral molecules, such as protein kinase R, are upregulated to either block or reduce viral infection [29]. Several studies show that treatment of susceptible human cells with IFN-α/β *in vitro* results in protection against HSV-2 replication [30,31]. Work from our own lab has shown that primary human genital epithelial cells, which are one of the first cells to encounter HSV-2 following acquisition or during reactivation, can be significantly protected against HSV-2 infection following treatment with ligands for TLR-3, -5 and -9 [32]. In animal models, inhibition of IFN-β signaling pathways is associated with increased HSV-2 viral burden and disease [33,34]. However, human biopsy studies reveal that extremely low levels of IFN-α and IFN-β are found in the genital tract during the course of HSV-2 infection, despite the presence of a large number of cells capable of synthesizing these molecules, raising questions about the importance of type I IFNs during the course of human HSV-2 infection [35].

In mice, natural killer (NK) cells have been implicated as potent anti-HSV-2 cells via their production of IFN-γ [36]. IFN-γ production can indirectly clear virus by inducing nitric oxide production, a potent obstructer of viral replication, from a multitude of cells [37]. Furthermore, studies involving NK and NKT cell deficient mice, showed a lower rate of survival and higher viral titers in the vaginal tract among HSV-2 infected mice [38]. The role of NK cells during the course of human HSV-2 infection, on the other hand, remains unclear. Earlier studies found low numbers of NK-like cells at the site of lesions [39], whereas later studies suggested a local enrichment of NK cells at the site of HSV lesions [40]. However, no apparent correlation between NK cell activity and viral clearance was found. Recent studies conducted on blood NK cells isolated from recurrent HSV-2 infected humans revealed that unlike infection with human CMV or HIV-1, HSV-2 infection does not drive blood NK cell differentiation toward a terminal effector status and leaves the NK cell receptor repertoire unaltered [41]. In mice, HSV-2 infection has also been associated with TLR9-mediated production of IFN-α by plasmacytoid dendritic cells (pDCs) [42]. Evidence from human studies suggest that pDCs are also essential in the innate antiviral response against HSV-2 and may play a role in activating T-cell responses against HSV-2 [42], a role typically relegated to conventional DCs (cDCs).

The role of adaptive immune system in containing HSV-2 during infection has been clearly established, as evidenced by the temporal correlation between the clearing of the virus and the number of infiltrating antigen-specific $CD4^+$ and $CD8^+$ T cells at the site of a lesion [40]. The importance of the host immune response is demonstrated by the severe, prolonged ulcerations that can occur in patients with AIDS [43] or after solid organ [44] or stem cell transplantation [45], where immune suppression is induced to prevent adverse outcomes such as rejection. In mice, $CD4^+$ T cells play key protective roles after whole virus vaccination, as shown by depletion studies [46,47]. $CD4^+$ T cells are an important source of IFN-γ, have cytotoxic effector activity for HSV-infected cells, and localize to human HSV-2 genital lesions [40]. In humans, herpetic ulcerations are also associated with the infiltration of large cytotoxic $CD8^+$ T-cell populations which are correlated with viral clearance [40]. Mathematical models predict that clinically the prolonged duration and increased severity of HSV shedding episodes is strongly associated with a low density of $CD8^+$ T cells in the genital mucosa [48]. B-cells contribute to the adaptive immune

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