Humoral and Cellular Immunity to Varicella-Zoster Virus: An Overview

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INNATE IMMUNITY

Under conditions of naturally acquired primary varicella-zoster virus (VZV) infection, the first response of the naive host is mediated by the innate immune system through antiviral cytokines and the activation of NK cells [1]. These responses are likely to be important for the initial control of VZV at mucosal sites of inoculation and to trigger the induction and amplification of adaptive, VZV-specific immunity. NK cells can lyse VZV-infected targets [2], and activated NK cells are a major source of interferon (IFN)–γ production, which enhances the clonal expansion of antigen-specific T cells. IFN-α inhibits VZV replication in vitro, and treatment with exogenous type I IFN-α reduced the severity of varicella in immunocompromised children with varicella [3]. In addition, VZV replication in skin is associated with extensive production of IFN-α by adjacent uninfected epidermal cells in the SCIDhu model of VZV pathogenesis; blocking this IFN-α response caused a dramatic increase in VZV spread in skin [4].

Innate mechanisms of immune control have the capacity to maintain the host-virus equilibrium, despite the VZV immune evasion strategies that inhibit both class I and class II major histocompatibility complex (MHC) mechanisms for antigen presentation to T cells while the virus is being transferred to skin and in early stages of cutaneous infection [4–6]. These strategies appear to be effective for delaying the acquisition of adaptive immunity; VZV-specific T cells were not detected during the incubation period and emerged gradually after the onset of the varicella rash, appearing in 12%, 31%, and 47% of healthy subjects with varicella who were tested at 1, 2, and 3 days after onset, respectively [7, 8]. Nevertheless, the acquisition of VZV-specific T cells appears to be necessary to prevent disseminated infection, as suggested by the risk of life-threatening varicella in children with malignancies or congenital T cell immunodeficiencies or who are receiving immunosuppression for organ transplantation, as well as to achieve resolution of the acute infection. Children with HIV infection are at risk for chronic varicella, which is consistent with an important role for VZV-specific cellular immunity [9]. High frequencies of T cells that lyse targets expressing VZV gE and immediate early (IE) 62 protein are detected in healthy subjects, but other viral proteins are also likely to be recognized by VZV-specific T cells during acute varicella [10]. The adaptive immune response to primary VZV infection also includes the induction of B cells that make VZV IgG and IgM antibodies, although the magnitude of this response does not correlate with the extent of varicella in healthy or immunodeficient children, and B cell immunodeficiencies do not appear to predispose to severe varicella [11, 12].

MEMORY IMMUNITY

The memory immune response that follows the resolution of naturally acquired primary VZV infection is characterized by the persistence of VZV IgG antibodies and, in most cases, VZV IgA antibodies, as well as VZV-specific CD4 and CD8 T cells [1]. VZV-specific IgG antibodies have been shown to bind many VZV proteins and function to mediate neutralization and antibody-dependent cytotoxicity. The overall frequency of
VZV-specific memory T cells with proliferative capacity has been estimated to be ~1:40,000 peripheral blood mononuclear cells [13]. These cells recognize VZV glycoproteins gE, gB, gC, and gH and the IE62 protein [7, 14, 15], and most produce IFN-γ and tumor necrosis factor–α [16]. Among these populations are MHC class I– or class II–restricted cytotoxic T cells that recognize VZV proteins, including include gC, gE, gI, and IE62 and IE63 proteins [10, 13, 17, 18]. In VZV-immune subjects tested ≥20 years after varicella, the mean ± SD frequency of memory cytotoxic T cells specific for IE62 was 1:105,000 ± 85,000, and that for gE was 1:121,000 ± 86,000.

The function of VZV IgG antibodies in protecting the host is presumed to be primarily the neutralization of infectious VZV at sites of inoculation on reexposure to the virus by contact with individuals who have varicella or herpes zoster (HZ). Should the virus evade this first line of defense as well as the local innate responses, it is likely that VZV-specific T cells are important for preventing symptomatic disease after exogenous reexposure. In addition, because VZV establishes latency in sensory ganglia, the adaptive T cell response is needed to prevent symptomatic reactivations of endogenous VZV. The common age-related decrease in VZV-specific T cells or a decrease resulting from immunosuppressive diseases or therapies is associated with an increased risk of HZ [19]. One hypothesis is that these exogenous and endogenous exposures to infectious VZV may promote the maintenance of robust VZV memory immunity, because household exposure to varicella often results in boosts in VZV humoral and cellular immune responses, and HZ stimulates a dramatic increase in VZV IgG antibodies and VZV-specific T cell frequencies [20, 21]. Alternatively, the persistence of memory immunity may result from the initial clonal expansion of VZV-specific T cells with helper and effector functions, without any requirement for subsequent restimulation in the immune host.

**VACCINE IMMUNITY**

According to current models, memory antiviral immunity is thought to be a consequence of the magnitude of the expansion of effector cell populations elicited by primary exposure to the pathogen [22] (figure 1). Memory immune responses are lower when the initial immunologic “burst” is limited, because virus-specific effector cell populations are normally regulated to decrease during the weeks to months after primary sensitization and expansion. The antigenic signal appears to be the most important factor in driving the expansion and, therefore, is expected to have direct consequences for the immunologic “set point” of the memory immune response. VZV immune responses peak within a few weeks after naturally acquired infection and decline to a persistent memory response with the characteristics described earlier. The capacity of the live attenuated varicella vaccine to elicit VZV IgG and T cell immunity in the naive healthy host was established in the prelicensure clinical evaluations of the vaccine [23]. As expected, the magnitude of these VZV-specific immune responses was related to the infectious virus content and to the antigen content of the vaccine preparation [24, 25]. Host factors also play a role, in that achieving responses in naïve adolescents and adults that were equivalent to those of younger children required the administration of 2 doses of varicella vaccine. However, providing 2 doses to younger children resulted in higher VZV IgG antibody titers and T cell proliferation responses, and some evidence, as reviewed by Watson [26] in this supplement, suggests that memory responses were sustained more effectively. This information has led to the recent recommendation to implement a 2-dose regimen of varicella vaccine in all age groups [27]. Because varicella epidemics have occurred annually in temperate climates and primary VZV infection appears to result invariably in the establishment of latent infection, with the potential for causing subclinical reactivation, it has not been possible to determine the relative importance of the primary host response and subsequent boosting for preserving protective immunity against VZV. By comparison with other live attenuated vaccines, such as measles vaccine, repeated exogenous or endogenous contact with wild-type VZV will probably not be required to maintain persistent immunity. However, the continuation of active and passive surveillance programs to monitor VZV infections in all age groups, as described in this supplement, will make it possible to determine whether additional booster doses of varicella vaccine should be given.

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