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Immune Responses to Varicella Zoster Virus and Effective Vaccines

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Varicella zoster virus (VZV) causes two distinct diseases, varicella (chickenpox) during primary infection, and herpes zoster (shingles) resulting from reactivation. The purpose of this review is to summarize the present understanding of VZV and the associated immune response, as well as to discuss available vaccines. VZV infection induces both innate and adaptive immune responses, especially an antigen-specific adaptive immune response, which activates humoral immunity and cell-mediated immunity (CMI). Reactivation of VZV can occur when the CMI of latent VZV is reduced, leading to herpes zoster. After VZV infection, natural killer (NK) cells modulate antigen presentation and the production of IFN-γ, an important activator of macrophages. IFN-γ is produced by NK cells and CD4 Th1/CD8 cytotoxic T lymphocytes. The T cell-mediated immune response is an important factor influencing VZV reactivation and herpes zoster, with herpes zoster being associated with reduced levels of VZV-specific T cells. Since the VZV-specific T cell population gradually declines with age, herpes zoster particularly affects the elderly. There are two types of zoster vaccines: live-attenuated and recombinant subunit. However, recombinant vaccines generally have poor immunogenicity when administered alone and require an adjuvant. Therefore, effective adjuvants are needed that especially promote cell-mediated immune responses. Various adjuvants have been developed, many of which enhance T cell immunity more than antibody-based humoral immunity. The information presented in this review may serve as a reference for future VZV immunology studies.

Key Words: Cell-mediated immunity, Herpes zoster, Humoral immunity, Varicella zoster virus, Adjuvants, VZV vaccine

INTRODUCTION

Varicella zoster virus (VZV), also known as human herpesvirus 3, belongs to the *Alphaherpesvirinae* subfamily and has a double-stranded DNA genome. VZV causes two distinct diseases, primary varicella infection (chickenpox) and herpes zoster (shingles). Herpes zoster develops from the reactivation of latent VZV in neurons of the cranial nerve ganglia, dorsal root ganglia, and enteric ganglia. Immunity to VZV is established after primary infection (1). Primary VZV infection induces both humoral and cellular immune responses, especially T-cell responses, which can prevent reactivation. Thus, cell-mediated immunity (CMI) is essential and is sufficient to prevent primary VZV infection in childhood and VZV reactivation in adults, the elderly, and immunosuppressed individuals (2, 3).

VZV DNA is present in respiratory secretions and fluid secretions from skin vesicles. It is transmitted through direct contact with skin lesions or respiratory secretions, or through inhalation of airborne virus particles (4). When a primary VZV infection occurs, the virus replicates in the epithelial cells of the upper respiratory mucosa and causes a vesicular rash after several days of incubation. Viral entry, via the direct fusion of viral particles with the plasma membrane, and viral spread begin when the infected T cells transport the virus to the skin. The reactivation of latent virus leading to viral replication in the ganglia causes the symptoms of herpes zoster (5).

The VZV genome is a linear double-stranded DNA molecule with 124 884 bp that encodes at least 71 unique open reading frames and related promoter sequences. The genome structure is similar to that of other alphaherpesviruses, consisting of a unique long region and a unique short region, each flanked by inverted repeats (6). The capsid of VZV is a regularly shaped icosahedron consisting of 20 triangular faces and 12 corners. The size of VZV ranges from 150-200 nm, and the envelope contains several glycoproteins that allow the virus to enter sensory nerve cells, where it replicates (7).

The proteins encoded by VZV DNA include five major viral glycoproteins, gE, gB, gH, gI, and gC, which are expressed on the membranes of infected cells during viral replication. These glycoproteins are recognized by T lymphocytes and are related to T-cell boosting. The immunological memory to these glycoproteins can be maintained long after primary VZV infection (8). Among these glycoproteins, VZV gE is the most abundant and most immunogenic. It is also the predominant protein expressed on infected cells. This viral glycoprotein elicits CMI and the formation of complement-dependent neutralizing antibodies. VZV gE as antigens contain conserved epitopes and elicit the induction of neutralizing and VZV gE-specific antibodies (9, 10).

The gE/gH-gI complex is a highly conserved core component of VZV envelope fusion during cell entry, and gE forms a stable heterodimer with gI for post-entry virus attachment and replication. Following viral fusion, entry, and replication, the immune response to gE is triggered (11). Because glycoproteins are critical for VZV entry and replication, and gE induces the production of VZV-specific antibodies, VZV gE has the potential to be used as a VZV subunit vaccine. Safe and effective vaccines have already contributed to lowering the incidence of VZV worldwide. However, live vaccines have the potential to reactivate and cause clinical disease, so recombinant protein vaccines that do not establish latency are attractive alternatives (12).

IMMUNOLOGY OF VZV INFECTION

The immune response can be broadly divided into innate and adaptive responses. Antigens are taken up by innate immune cells such as dendritic cells (DCs) that migrate to the T-cell region of the draining lymph node to combat infection. The adaptive immune response involves T cells and B cells. B cells produce antibodies, and helper T (Th) cells release cytokines to boost CMI (13). Primary VZV infection induces both innate and antigen-specific adaptive immune responses in healthy individuals. Innate immunity may limit the initial spread of VZV within the host, but the VZV-specific adaptive immune response induced by humoral and CMI plays a crucial role in the recovery from varicella and the prevention of VZV reactivation (14). Antiviral drugs and vaccines against both varicella and zoster are available and effective in treating and preventing VZV-induced diseases (15).

Primary VZV Infection

Varicella occurs mainly in childhood and can be severe in immunocompromised individuals, infants, and adults. During primary infection, VZV is directly transported from mucosal sites to regional lymph nodes, and ultimately to the skin, leading to skin infections. This transport process appears to occur because DCs are permissive to VZV and infected DCs can transmit the virus to T lymphocytes. Through these various virus-host cell interactions, the virus induces a host immune response and causes disease (16).

During primary exposure to VZV, the first response of the naive host is mediated by the innate immune system through antiviral cytokines and activated natural killer (NK) cells. As effectors of innate immunity, NK cells have the ability to recognize and kill infected cells in the absence of antibodies and major histocompatibility complexes (MHCs). NK cells also play a role in the adaptive immune response and establishment of immunological memory. Eventually, NK cells activated by VZV infection modulate antigen presentation and type I interferon (IFN-I) production, which enhances the clonal expansion of antigen-specific T cells (17).

IFNs are key antiviral cytokines that are critical for establishing innate and adaptive immunity against viral antigens. The innate immune response to VZV involves the recognition of viral pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs), which triggers the activation of several signaling cascades in the host immune cells, such as the stimulation of IFNs or other cytokines (18). Additionally, PAMPs are recognized by toll-like receptors (TLRs), among which TLR3 plays a fundamental role in pathogen recognition and innate immunity activation. TLR3 is known to be expressed in human neurons and may play a pivotal role in controlling VZV spread in the nervous system (19).

VZV Reactivation

After primary infection, latency can be established in the ganglia. As cellular immunity to VZV wanes with advancing age or in immunocompromised individuals, latent VZV reactivates, causing zoster. Antigen-specific T cells are associated with infected neurons and the T cells retained in the ganglia inhibit reactivation of the latent virus. Although antibodies prevent primary VZV infection, VZV-specific T cells are essential for preventing reactivation by controlling latency (20) and the reduction in the number of these immune cells facilitates the development of herpes zoster. VZV-specific T cells are generated by DCs, but when DCs become infected, VZV can evade the antiviral immune response (21).

The incidence and severity of herpes zoster is increased in elderly adults and immunocompromised people. Specifically, ~68% of herpes zoster cases occur in individuals of over 50 years of age (22). This trend results due the population of VZV-specific T cells gradually declining with age, leading to reduced CMI. After primary infection, CMI conferred by CD4+ and CD8+ T cells controls the replication and reactivation of latent VZV in the ganglia (23). However, like the VZV-specific T cell population, CMI diminishes with age and zoster can develop when CMI falls below a critical level (24). Therefore, the T cell-mediated immune response is intimately involved in the reactivation of VZV. Unlike T-cell immunity, anti-VZV antibody levels remain relatively stable with age, indicating the humoral immune response mediated by antibodies may not be sufficient to prevent VZV reactivation (25). Approved VZV vaccines can boost VZV-specific CMI, thereby preventing the reactivation of VZV and ultimately reducing the severity of herpes zoster.

Humoral and Cellular Immunity

Viral replication during infection is controlled by both innate and adaptive immune responses mediated by NK cells and interferon-gamma (IFN-γ) cytokines. The correlation between increased VZV reactivation rates and increased age is mainly due to the decreasing numbers of T cells, rather than to the decreased humoral immunity. The adaptive immune response to primary VZV infection includes the activation of B cells that produce VZV antibodies such as IgG and IgM; however, immunological memory may persist via the initial clonal expansion of VZV-specific T cells (26). T cells are essential for resolving VZV disease, limiting its severity, and preventing reactivation, while humoral immunity conferred by antibodies is important for preventing primary VZV infection (27).

Helper T cells (Th cells), also known as CD4+ cells, play an important role in the immune system by contributing to both cellular and humoral immunity. They stimulate the activity of other immune cells by releasing T-cell cytokines, helping to suppress and regulate immune responses. Th cells are essential for the production of B-cell antibodies, activation of cytotoxic T cells, and promotion of antibacterial activity of macrophages and other phagocytic cells. Th cells recognize and are activated by antigens presented through MHC class II molecules of antigen-presenting cells. Th cells can be subdivided

into Th1 and Th2 cells. Th1 cells are related to CMI, while Th2 cells assist antibody production via cytokines. Th1 cells produce IL-2, IFN-γ, and tumor necrosis factor-alpha (TNF-α), which promote cytotoxic T cell reactions and delayed-type hypersensitivity. Th2 cells produce IL-4, IL-5, IL-6, IL-10, and IL-13, which assist B cell responses and allergic reactions (28).

Cytokines have an important role in inhibiting the spread of VZV after primary infection. Th1-type adaptive immunity might play a major role in VZV infection. The increased concentration of cytokines is responsible for the activation of humoral and cell-mediated immunity (29). The production of TNF-α and IL-12 is increased in the acute phases of varicella and zoster. IFN-γ is a cytokine that is critical for innate and adaptive immunity, and TNF-α and IL-12 mediate the induction of IFN-γ production (30). The immune response activated by cytokines such as IFN-γ, IL-10, and IL-12 can be detected during the initial development of VZV immunity.

IL-12 acts as a proinflammatory cytokine that promotes Th1 responses by enhancing IFN-γ, increasing IL-2 receptor expression, and inhibiting IL-4 production. IL-12 also supports the proliferation of antigen-stimulated T cells (31). As a T cell-stimulating factor, IL-12 can induce the growth and function of T cells, increasing the production of IFN-γ and TNF-α by T cells and NK cells and reducing IL-4-mediated suppression of IFN-γ. VZV-specific CD4+ T cells synthesize Th1-like cytokines, such as IL-2 and IFN-γ, and induce CD8+ T cell-mediated cytotoxicity (32, 33).

VZV antibody is an important factor in varicella prevention, but it is insufficient for preventing herpes zoster. CMI and VZV antibodies are both increased in response to zoster vaccines. However, there seems to be no correlation between the two immune responses. Furthermore, it has been shown clinically that a high level of CMI is more effective than a high antibody level in preventing zoster caused by the reactivation of VZV (34). Direct interactions between T cells and neurons or a rapid T-cell response may prevent VZV reactivation from reaching clinically apparent levels (35).

HERPES ZOSTER VACCINES AND IMMUNE RESPONSE

Primary VZV infection leads to latency in the sensory ganglia and activates CMI, which eventually prevents the reactivation and spread of VZV. However, VZV-specific CMI gradually declines with age. The increased incidence and severity of herpes zoster in older populations indicates that aging or immunosuppression is related to the reactivation of latent VZV. The incidence and complications of herpes zoster can be reduced by vaccination (36). A vaccine capable of boosting pre-existing VZV-specific CMI responses in subjects with decreased immunity may therefore prevent VZV reactivation.

Currently, three herpes zoster vaccines have been approved worldwide. Two are live-attenuated vaccines (LAVs) for zoster, licensed in 2006 (Zostavax) and 2017 (SKYZoster), and the other is a recombinant vaccine for zoster approved in 2017 (Shingrix). These vaccines are able to enhance VZV-specific CMI, reducing the incidence and severity of disease. The LAVs are derived from the Oka strain of VZV created by Dr. Takahashi in 1974. The dose administered to prevent zoster is 14-fold greater than that used to prevent varicella. These vaccines stimulate VZV-specific antibody production and T-cell immunity (37). The LAVs derived from Oka strain are safe and highly effective but are not sufficient to establish herd immunity against VZV. Moreover, similar to natural infections, the virus in the LAVs can remain latent in the dorsal root ganglia and reactivate (38). Therefore, there is a need for additional VZV vaccines that will elicit a strong immune response without establishing virus latency.

Shingrix, a liposome-based recombinant subunit vaccine developed as an alternative to LAVs, contains VZV gE. VZV gE, the most abundant and immunogenic viral glycoprotein, elicits CMI and the formation of complement-dependent neutralizing antibodies (39). Both humoral and cell-mediated responses to gE have been observed following virus infection (40). However, VZV gE alone does not induce a strong CMI response. Therefore, adjuvants such as AS01B were combined with gE and added to the recombinant zoster vaccine. AS01B is an adjuvant system that combines *Quillaja saponaria* Molina (QS21), a plant saponin, and monophosphoryl lipid (MPL), a TLR4 agonist. These adjuvant components stimulate antibody production and synergistically enhance VZV gE-specific CMI (41). Therefore, the recombinant zoster vaccine with an

adjuvant to boost CMI may induce strong immunologic responses to VZV (42). This vaccine has great potential to improve clinical efficacy when combined with the adjuvant AS01B (38).

VZV-specific T-cell responses are greater in response to the recombinant subunit vaccine than to the LAVs, whereas cytotoxic responses by CD8+ T cells and effector T cells are greater in response to the LAVs (43). Because IL-2 and IFN-γ are important in VZV-specific CMI, they have been analyzed in context of the vaccines. The recombinant zoster vaccine with adjuvant generates significantly higher VZV-specific IL-2 and gE-specific IL-2, IFN-γ, and IL-2/IFN-γ peaks compared to those of the LAVs. Furthermore, the recombinant vaccine generates higher memory and effector memory CD4+ responses (44).

ADJUVANTS

Vaccines are typically composed of antigens and adjuvants formulated as emulsions. LAVs do not require adjuvants as they cause a mild infection and an immune response that is very similar to that which occurs after infection with wild-type virus. However, recombinant purified proteins generally need an adjuvant to increase their immunogenicity in order to increase antibody levels and generate T-cell memory that confers immunity for longer periods of time (45, 46). Adjuvants also induce the priming of antigen-specific Th cells that produce Th1, Th2, and Th17 cytokines and promote the activation of innate immunity (47).

Recombinant vaccines require effective adjuvants that promote both cell-mediated and innate immune responses. Some adjuvants can enhance the efficacy of a vaccine by activating T cells instead of antibody-secreting B cells, depending on the purpose of the vaccine (48). For instance, because herpes zoster is related to the reduction in VZV-specific T cells, various adjuvants have been developed as immune boosters or delivery systems that are more focused on enhancing T-cell immunity than antibody-based humoral immunity.

Adjuvants are conventionally classified into several categories: mineral compounds, bacterial products, oil-based emulsions, virosomes, immune stimulating complexes, virus-like particles, and liposomes. Of these, aluminum-based mineral compounds are the most widely used and are the preferred choice for treating humans. Oil-in-water emulsion adjuvants, such as squalene-based MF59 or AS03, are known to mainly enhance the antigenic immune response and cause greater Th1 immune responses than that of aluminum-based adjuvants, which cause Th2 immune responses (49, 50).

Table 1. Adjuvant types and immune effects

Components	Adjuvant	Uses	Immune Effects
Mineral salt	Alum	Various vaccines	Safe, Th2 responses
Squalene	MF59	Influenza	Promotes antigen uptake, migration of cells to lymph nodes
Squalene	AS03	Influenza (pandemic)	Recruitment of innate cells
Alum+MPL	AS04	HBV, HPV	Stimulate TLR-4
Oligodeoxynucleotide (TLR-9 agonist)	CpG	COVID19	Strongly activate B cells and TLR9-dependent NF-κB signaling
Vesicles incorporating virus derived proteins	Virosome	Hepatitis / Influenza	Increase uptake by APCs, interact with B cells
Saponin+MPL	AS01	Zoster	Strong Th1 responses
Cytokine	Interleukin	Cancer / HIV	Induces cytokines
Immunostimulatory complexes (QuilA+Cholesterol+lipid)	ISCOM	Equnine influenza / FeLV	Induces CTL immune responses
PLGA, poloxamer, polyanhydrides	Microsphere	NA	Easily transfer to APC on mucous membrane

Novel vaccine adjuvants such as PRR agonists have also been developed that induce a balanced Th1/Th2 response. In particular, PRR agonists stimulate TLRs and induce cytotoxic T-lymphocyte responses, resulting in a strong immune reaction. Recently developed complex immune boosters include PolyI:C (TLR3), GLA-SE (TLR4), imidazoquinolines (TLR7/8), and CpG oligonucleotides (TLR9) (13) (Table 1). For vaccines in which the antibody-like immune response alone does not provide a sufficient protective effect, more effective adjuvants are being developed that are based on PRR agonists known to induce strong CD8+ T-cell responses and based on immunity enhancing agents such as ISCOMATRIX (51).

CONCLUSION

VZV establishes latency in sensory ganglia after primary infection, similar to herpes simplex viruses 1 and 2 (HSV-1 and HSV-2) and reactivates in elderly or immunocompromised populations. Due to its longer clinical efficacy, the level of CMI is more important than the level of antibody for preventing zoster as the interaction between T cells and neurons in the ganglia can mitigate VZV reactivation. VZV antibody responses have been shown to be extremely stable with age, unlike the number of VZV-specific T cells. Therefore, the ability to confer VZV-specific CMI must be a key attribute of herpes zoster vaccines (52).

As an alternative to LAVs, recombinant subunit vaccines with strong immunogenicity have been developed. VZV gE is an attractive candidate as a subunit antigen for herpes zoster vaccines due to its abundance during natural infection and ability to induce VZV-specific antibody production and CD4+ T-cell responses. However, recombinant subunit zoster vaccines need adjuvants to enhance their ability to strongly elicit innate and adaptive immune responses. Therefore, an effective subunit vaccine with a potent adjuvant that induces high Th1/Th2 immune response is rapidly replacing the LAVs. Through this review, we hope to provide insight into the current understanding of the immune response to VZV, which may be helpful in the development a stronger and more effective vaccine.

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CONFLICT OF INTEREST

All authors declare the following interests: SJL and HK are SK bioscience employees and may hold stock. KJH and JHN have no interests.

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DISCLOSURE

The authors declare no conflicts of interest for this article.

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