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Review Article

Update on Varicella Zoster Virus Infections with Focus on the Reported Beneficial Effects of the Virus

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Abstract

Varicella zoster virus (VZV) behaves differently from other herpes viruses as it differs from them in many aspects. Recently, there has been increasing reports on the beneficial effects of the virus in immunocompromised hosts and neurodegenerative disorders these reports include: stimulation of bone marrow (BM) function manifested by increase in white blood count, hemoglobin level, and platelet count in patients with hematologic malignancies (HMs) and BM failure syndromes; BM biopsy proven reversal of pure red cell aplasia by concurrent VZV infection; VZV infections in patients with multiple myeloma subjected to autologous hematopoietic stem cell transplantation (HSCT) causing longer overall survival (OS) compared to myeloma patients who did not have the infection; reactivation of VZV in patients with various HMs subjected to allogeneic HSCTs was associated with not only improved OS but also reduced rate of relapse of the primary disease; engineered VZV served as oncolytic virus; the inverse relationship between VZV infection the incidence of glioma; association with graft versus host disease which has anticancer effects; several reports of cure or prolonged control of various HMs and solid tumors with no or light chemotherapy due to concurrent VZV infections; and association between VZV vaccination and lower incidence of dementia and neurodegenerative disorders.

In this review, after highlighting VZV infections and the peculiar features of the virus, the following topics will be thoroughly discussed: immunology and pathogenesis of VZV infections; hematopoiesis and BM microenvironment, VZV vaccines with reports on the safety of the vaccines in immunocompromised hosts; and oncolytic viruses with the future role of VZV. Also, possible explanations of the beneficial effects of VZV will be provided.

Keywords: Varicella zoster virus; Vaccines; Hematopoiesis; Mesenchymal stromal cells; Cellular proteins; Cytokines; Signaling pathways; Oncolytic virotherapy

Introduction

Varicella-zoster virus (VZV) is a highly contagious alpha-herpesvirus, with a double- stranded DNA genome, that only naturally infects humans [1-3]. Chickenpox, which mainly affects children, is the outcome of primary infection with VZV while reactivation of the latent VZV takes the form of herpes zoster (HZ) that may occur decades later and affects immunocompromised individuals [1-3]. The risk factors for reactivation of VZV include in adults include: old age; distress; recipient of hematopoietic stem cell transplantation (HSCT) and solid organ transplantation; hematologic malignancies (HMs) such as leukemias and lymphomas; solid tumors; certain infections such as human immunodeficiency virus (HIV) and coronavirus disease (COVID-19); patients with cellular immune deficiency; and patients on immunosuppressive therapies such as: prednisone, azathioprine, mercaptopurine, methotrexate; and tumor necrosis factor inhibitors [4-6]. VZV infection may present as self-limiting illness with minor complications such as transient pancytopenia but can also lead to serious consequences such as: aplastic anemia, post-herpetic neuralgia, severe pneumonia, meningoencephalitis, cranial nerve palsies, myelitis, motor weakness, Guillain-Barré syndrome, stroke, in addition to an illness mimicking giant cell arteritis [1,2].

The diagnosis of VZV infection is usually made on clinical grounds based on the presence of the characteristic skin lesions of chickenpox or HZ followed by examination of the vesicular fluid [2,7-9]. However, additional diagnostic techniques may be needed to confirm the diagnosis and these include: (1) virus isolation by Tzanck smears, electron microscopy, antigen detection, viral culture, and direct fluorescent antibodies on scrapings obtained from active skin lesions; (2) serologic assays for immunoglobulin G, M or A class antibodies using enzyme linked immunosorbent assay (ELISA); and (3) real-time polymerase chain reaction (RT-PCR) which has higher sensitivity than serological assays [2,7-10]. The currently available serological tests to detect VZV-specific antibodies are exclusively based on antigens derived from VZV-infected cells. However, serological differentiation between chickenpox and herpes zoster may be possible by analysis of the IgM-portfolio against individual viral antigens [11]. The LightCycler PCR for detection of VZV has the following advantages: very high sensitivity, rapid turnaround time for reporting results, virtual elimination of amplicon carryover contamination, and equivalent costs compared to shell vial cell culture for detection of the virus [12]. Although theoretically possible, isolation of VZV DNA

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from human BM aspirates has rarely been achieved by molecular techniques such as quantitative PCR and next-generation sequencing (NGS) [13-15].

Acyclovir, valacyclovir, and famciclovir which have been approved by the food and drug administration (FDA) in United States of America (USA); brivudine which is used in some European countries; and the helicase-primase inhibitor (amenamevir) which has been approved in Japan represent the cornerstone of treatment of VZV infections worldwide despite having safety concerns about the use of brivudine and amenamevir [5,16-18]. Additionally, valnivudine hydrochloride, valomaciclovir stearate, and pritelivir have been shown to be effective in the treatment of HZ [16,18]. Although brivudine has been used in the treatment of HZ for years, a meta-analysis that included 7 randomized clinical trials (RCTS) showed evidence of effectiveness without sufficient evidence on safety of the drug in the treatment of HZ [17].

Varicella Zoster Virus: Structure and Peculiar Features

VZV is a human neurotropic virus which is highly contagious. It is an exclusively human pathogen. Hence, it is extremely difficult to find an animal model for the virus [2,19]. VZV is a double stranded DNA virus that belongs to the alpha group of herpes viruses. VZV genome, approximately 125,000 base pairs in size, which is the smallest genome among herpes viruses has approximately 74 open reading frame (ORF) proteins and it consists of a linear double-stranded DNA molecule [20-23]. VZV genome has lost almost all the genes that are not essential for its survival over approximately 70 million years of evolution [22]. The virion is composed of an icosahedral nucleocaspid; that harbors the DNA genome; surrounded by a tegument layer which is covered by an envelope derived from the host cell or a plasma membrane with incorporated viral glycoproteins [20-23]. A cross-sectional view of VZV genome is shown in Figure 1 [9,20-23]. Having high proliferation rates and relatively small genomes allow viruses to accumulate mutations and continuously present the host with new challenges. Consequently, viruses either escape detection or modulate host physiology often by redirecting cellular pathways to their own advantage [24].

Compared to other herpesviruses, VZV has the following peculiar features: (1) being an exclusively human pathogen, with no animal reservoir; (2) having the smallest viral genome;

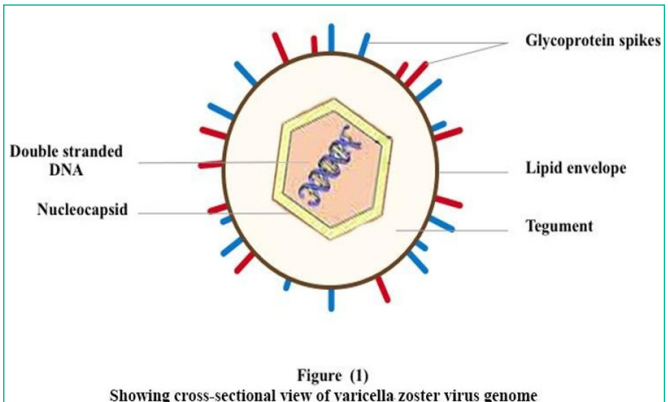

Figure 1: Showing cross-sectional view of varicella zoster virus genome.

(3) it encodes no inhibitors of autophagy; (4) over its long-standing evolution, the VZV genome has lost all genes that are not essential for its survival; (5) being extremely cell- associated and it spreads almost exclusively via cell membrane fusion; (6) ability to induce inflammatory pathway and cytokine profiles in a toll-like receptors-2 dependent manner; and (7) being the only human herpesvirus for which vaccines have been developed to reduce morbidity and mortality from both primary and recurrent infections [1,22,25-29].

The Reported Beneficial Effects of Varicella Zoster Virus

VZV has been reported to behave differently from other members of the herpesviruses group and there is growing evidence showing certain beneficial effects of the virus in immunocompromised hosts and these effects can translate into prolongation of overall survival (OS) [25,30-38]. In a single center, case-controlled, retrospective study published in 2005 that included 16 episodes of VZV infection occurring in 14 patients with various types of HMs and bone marrow (BM) failure syndromes subjected to various forms of immunosuppressive therapies, cytotoxic chemotherapy and HSCT, Al-Anazi KA, et al. reported an increase in white blood cell count (WBC), hemoglobin level (Hb), and platelet count (PLT) starting approximately 6 weeks following VZV infection and this increase in the three blood indices was maintained for periods longer than 3 years after VZV infection [25]. This study was the first world report that clearly showed stimulation of BM function by VZV infection starting 6 weeks after the infection and lasting for several years thereafter. The authors postulated that immunological changes induced by VZV infection particularly cytokine release could be responsible for stimulation of BM activity by VZV infection [25]. In the year 2019, Al-Anazi KA, et al. reported reversal of pure red cell aplasia (PRCA) by VZV infection [30]. A patient with BM biopsy proven PRCA was initially treated with cyclosporine-A and prednisolone, but this treatment was discontinued due to intolerance reported by the patient. Two months after stopping immunosuppressive therapy, the patient developed localized HZ infection that was successfully treated with valaciclovir. Six weeks after the VZV infection, Hb level started to increase gradually till the patient became packed red blood cell transfusion independent few months later. The steady increase in Hb level continued till it plateaued about 14 months after VZV infection. A repeat BM biopsy showed total resolution of the PRCA and regeneration of the erythroid precursors in the BM [30]. Interestingly, this report confirmed not only the time line for VZV to start its effect on the hematopoietic precursors in the BM, but also confirmed, from laboratory point of view, that VZV infection causes stimulation of BM function in patients with HMs and BM failure which may last for years [30].

In single center retrospective study that included 191 patients with multiple myeloma (MM) initially treated with cytotoxic chemotherapy, bortezomib-based or thalidomide-based therapy then subjected to high dose melphalan followed by autologous HSCT, Kamber C, et al. reported that approximately 30% of these patients developed VZV infections either before or after autologous transplantation [31]. VZV infections were encountered more frequently in patients with advanced stage MM, renal failure and relapsing disease [31]. Despite encountering VZV infections in patients with worse expected prognosis, the OS in patients who developed VZV infection

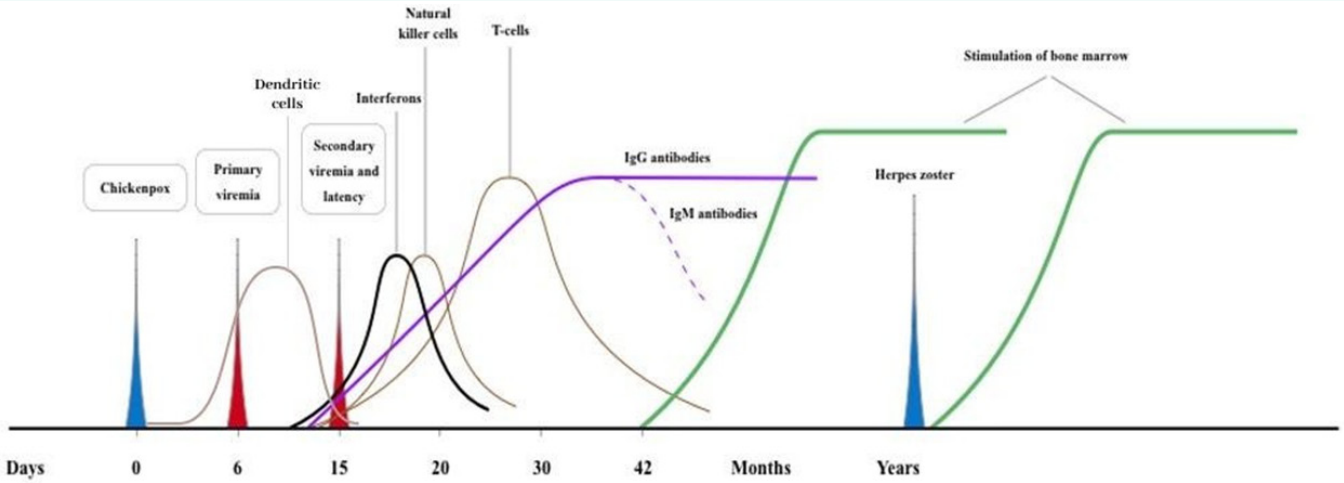

Figure 2: Timeline for the pathological events and bone marrow consequences of varicella zoster virus infection.

was superior to that in patients who never developed the infection. Additionally, there was no delay in neutrophil recovery after HSCT in patients infected with VZV and PLT count recovery post-HSCT was reported to occur earlier in patients infected with VZV [31]. Also, in a recently published study that included 219 patients with HMs (acute and chronic leukemia as well as myelodysplastic syndromes) subjected to allogeneic HSCT, Li P et al showed that VZV reactivation following allogeneic HSCT was an independent predictor for lower relapse rates and improved OS, thus providing novel therapeutic approaches to improve the long-term survival of patients following allogeneic HSCT [32].

In a recently published study in an animal model, Jiang H et al. demonstrated that Ellen Laboratory Strain of VZV engineered with deletion of ORF gene and addition of interleukin (IL)-12 can be used as a novel VZV-based oncolytic virotherapy [33]. Also, Chtioui H, et al. reported that a pediatric patient with B-cell acute lymphoblastic leukemia (ALL) had chickenpox at presentation of his leukemia. So, chemotherapy was held and acyclovir therapy was initiated. At the time of chickenpox resolution, the patient was found to have spontaneous partial remission of his ALL and the authors attributed the response to acyclovir therapy [34].

Multiple studies have demonstrated that VZV exposure or infection is inversely correlated with the risk of glioma and that VZV exhibits an intrinsic oncolytic potential in malignant glioma cell cultures and might be a novel candidate for virotherapy in glioblastoma multiforme (GBM) [35-37]. Additionally, several studies have shown that VZV infection may trigger chronic graft versus host disease (GVHD) following allogeneic HSCT [38-40]. It is well recognized that, provided GVHD is of low-grade, it may induce graft versus cancer effects and can be associated with improvement of OS in patients with acute leukemia or lymphoma [41-43]. Khoury LM, et al. reported complete response (CR) of a heavily pre- treated, advanced maxillary sinus squamous cell cancer with distant metastases in an elderly patient after 3 doses of immune checkpoint inhibitors (ICIs). Meanwhile, the patient developed severe HZ infection and no more ICIs were administered. The exceptional response was confirmed with imaging studies and it lasted longer than 5 years. As the documented cases of cancer patients who achieved CR after few doses of ICIs are rare, the authors attributed the long-lasting remission to the oncolytic effect of VZV [44]. Köstek O, et al reported an elderly patient with newly diagnosed undifferentiated pleomorphic sarcoma involving chest wall with bilateral pleural metastasis. The patient had VZV infection, at presentation of his cancer, which was treated with brivudine. The patient did not receive any specific treatment for his metastatic sarcoma such as cytotoxic chemotherapy. Surprisingly, the patient had almost CR of his sarcoma and this response lasted for 27 months. The authors attributed the control of metastatic sarcoma to brivudine treatment [45]. Some studies have shown epidemiological association between viral infections including VZV infection and the risk of dementia [46-48]. However, several studies and one meta-analysis have shown that VZV vaccination, particularly the recombinant subunit HZ vaccine, decreases the risks of dementia, Alzheimer's disease, Parkinson's disease (PD) and other neurodegenerative disorders [46,47,49-52]. In order to draw the attention of scientists to the beneficial effects of VZV in patients with BM failure and hematologic malignancy, Al-Anazi KA, et al. published several articles including a review article in which they suggested a possible pathogenesis of VZV infection and they drew a timeline for the pathological events and BM consequences of VZV infections [9,53-55]. The timeline of the pathological events and the consequences of VZV infections on BM function is shown in Figure 2 [9,53-55].

Immunology and Pathogenesis of VZV

Animal and Other Disease Models of VZV Infection

VZV pathogenesis, latency, and reactivation are difficult to study due to the fact that VZV is an exclusively human pathogen [56-58]. Numerous efforts have been made to develop adequate animal models of VZV infection but these models remain limited because all aspects of VZV infection, latency and reactivation, as well as the knowledge on the pathogenesis of VZV will remain incomplete without a suitable model [56,58]. Given that VZV infection is highly specific to humans, developing a reliable in vivo model that recapitulates the hallmarks of VZV infection has been challenging [59]. Simian varicella virus (SVV) infection of rhesus macaques (RM) closely resembles both human primary VZV infection and reactivation, with analyses at early times after infection providing valuable information about the extent of viral replication and the host immune responses [60].

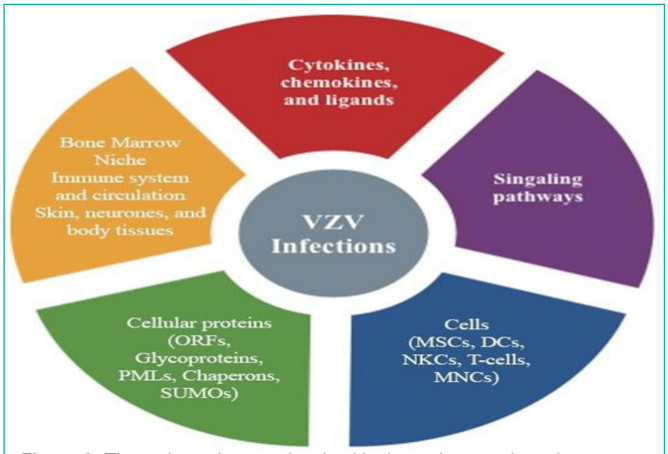

Figure 3: The various elements involved in the pathogenesis and consequences of VZV infections.
VZV: Varicella Zoster Virus; ORF: Open Frame Reading; PML: Promylocytic Leukemia Protein; SUMO: Small Ubiquitin-like Modifier; MSC: Mesenchymal Stem Cell; DC: Dendritic Cell; NKC: Natural Killer Cell; MNC: Mononuclear Cell.

SVV infection in nonhuman primates, such as RM, reproduces the cardinal features of VZV infections in humans and provides a model to investigate VZV pathogenesis and antiviral strategies because: (1) the VZV and SVV genomes are similar in size and structure and share 70-75% DNA homology, (2) the DNAs of SVV and VZV are co-linear in gene arrangement with the exception of the left end of the viral genomes, and (3) during viral latency, gene expression of VZV and SVV is limited to transcription of a viral latency- associated transcript (LAT) [59,61,62]. Hence, VZV and SVV are closely related alpha herpesviruses and it is likely that they arose from an ancestral varicella virus which evolved through cospeciation into species-specific viruses [61]. Three-dimensional normal human neural progenitor tissue-like assemblies (NHNP-TLAs) constitute an effective system to investigate long-term interactions of VZV with complex assemblies of human neuronal cells [57]. Human induced pluripotent stem cell (hiPSC)-derived neural cell culture models are an emerging tool to investigate VZV neuro-immune interactions [63]. For example, hiPSC- derived neurospheroids display functional innate immune reactivity towards Sendai virus infection, and have the capacity to recapitulate the strong immune evasive behavior towards VZV [64]. Advances in the development of in vitro human neuron systems for modeling VZV latency and reactivation and the recent discovery of the VZV-LAT have set the stage for a new era in resolving this perplexing persistent state [65].

The Cells Involved in VZV Infection

During infection, mesenchymal stromal cells (MSCs) have the following roles: (1) detection of pathogens, (2) activation of host immune responses, (3) elimination of pathogens, (4) induction of proinflammatory gradients, and (5) modulation of proinflammatory host immune response [66,67]. MSCs play a critical role in response to infection by: initiating removal of cell debris, exerting major immunoregulatory activities, and controlling pathogens [68]. On the contrary, MSCs may constitute immune privileged sanctuaries for certain pathogens such as viruses and Mycobacterium tuberculosis [68-71]. Studies have shown that MSCs are highly permissive to infection by herpesviruses including VZV [67,72,73]. One study showed that human MSCs were found to be suitable for targeting VZV to sites of tumor growth of GBM and that VZV replicated efficiently in glioma cells and this was followed by rapid oncolysis in vitro [74]. Natural killer (NK) cells, which are cytotoxic innate lymphocytes that exert a significant influence on the control of viral infection, play a crucial role in the immune system and may have a potential role in the pathogenesis of VZV [75,76]. VZV can productively infect human NK cells through cell-cell interaction and this infection: (1) can lead to the development of a characteristic phenotype that promotes the migration of infected cells towards the skin, and (2) may potently impair the ability of NK cells to respond to target cell stimulation in vitro, leading to a loss of both cytotoxic and cytokine responses [75-77]. VZV ORF4 has a novel function in limiting NK cell-mediated cytotoxicity through a granzyme B cleavage site-independent mechanism [78].

Mature dendritic cells (DCs) are potent antigen-presenting cells that are essential for initiating successful antiviral immune responses and would therefore serve as an ideal target for viruses seeking to evade or delay the immune response by disrupting their function [79]. Several studies have shown that mature DCs are permissive to VZV and infection of DCs infection reduces their ability to function properly and can lead to transmission of the virus to T lymphocytes allowing VZV to evade the antiviral immune response and that VZV-infected T cells subsequently spread infection throughout the body to give the typical varicella skin rash [79-81].

T-cells, peripheral blood mononuclear cells (PB-MNCs), and B cells are also permissive to VZV infection [82]. Studies have shown that VZV ORF47 is essential for VZV replication in human T cells, and that VZV infection of T cells can mediate transfer of the virus to skin [83,84]. Human monocytes, which are highly abundant in the circulation, are permissive to productive VZV infection [85]. Sialic acid-binding immunoglobulin-like lectin (Siglec)-7 is required for VZV infection of human monocytes [86]. VZV infection of monocytes modulates their function and helps to disseminate the virus to different body parts during primary infection (chickenpox) [82,85,87]. The dysfunction of host's lymphocytes and activation of Toll-like receptors (TLRs) in PBMCs are important mechanism in VZV- induced HZ. Hence, TLRs might be potential therapeutic targets in drug development for the treatment of HZ [88]. VZV infection influences the antigen presentation potential of monocytes, and substantially impacts monocytes longevity and ability to generate site- specific macrophages [89].

The Cytokines, Chemokines, and Ligands Involved in VZV Infection

VZV induces cellular activation of inflammatory cytokine pathways in a species-specific, TLR-2-dependent manner [28]. Multiple studies have shown that the following cytokines are expressed or elevated in the serum following VZV infections: IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, IL-21, IL-23, and IL-1β in addition to interferon-alpha (IFN-α) and IFN- gamma (γ) as well as VZV immunoglobulin (Ig)G antibodies [90-100]. Both type I and type II IFNs have been implicated in the host defense against VZV. However, IFN-γ has more potent activity than IFN-α against VZV [101]. VZV infection induces the expression of suppressor of cytokine signaling-3 (SOCS3) resulting in modulation of type I IFN signaling and viral

replication [102]. VZV encodes an immunomodulatory function which directly interferes with the IFN-γ signal transduction via the JAK/STAT pathway and enables the virus to inhibit IFN-γ induction of cell surface major histocompatibility complex (MHC) class II expression [103]. VZV implements multiple mechanisms targeting both CD1d transcript and protein [104]. VZV induces formation of the nucleotide-binding oligomerization domain (NOD)-like receptor (NLRP)-3 inflammasome and the associated processing of the proinflammatory cytokine IL-1β by activated caspase-1 in cells infected by the virus [105]. The viral particles of VZV particularly glycoprotein C enhance chemokine-dependent T-cell or leukocyte migration [106]. Chemokines and matrix metalloproteinases are elevated in the cerebrospinal fluid (CSF) of patients with VZV central nervous system (CNS) infections [107]. Studies have shown that VZV suppresses both the programmed death ligand 1 and the MHC-1, class I-related biosynthesis pathway in various cell lines [108,109]. The nonclassical antigen presentation molecule CD1d presents lipid antigens to invariant NK-T (iNKT) cells. However, activation of iNKT cells triggers a rapid cytokine response providing an interface between innate and adaptive immune responses [104,110]. VZV implements multiple mechanisms targeting both CD1d transcript and protein and the virus interacts with and manipulates the CD1d-iNKT cell axis [104].

The Signaling Pathways Involved in VZV Infections

Multiple studies have shown that several signaling pathways are involved or activated in VZV infections and these include: (1) Janus kinase/signal transducer and activation of transcription (JAK/STAT) pathway; (2) c-Jun N-terminal Kinase (JNK) pathway; (3) extracellular signal-regulated kinase (ERK/MEK) pathway; (4) phosphatidylinositol 3- kinase (PI3K/Akt) pathway; (5) nuclear factor kappa B (NF-κβ) pathway; (6) mitogen- activated protein kinase (MAPK) pathway; (7) Wnt-Wingless pathway; (8) stimulator of interferon genes (STING) pathway; and (8) cyclic AMP response element binding protein (CREB) pathway. However, JAK/STAT signaling is the most studied pathway [111-123].

Open Reading Frames in VZV Infections

The double-stranded VZV genome contains approximately 125,000 base pairs including approximately 74 ORFs of which 11 encode for glycoproteins [23,124-127]. During latency, VZV expresses at least 6 ORFs and these include: ORF 4, ORF 21, ORF 29, ORF62, ORF63, and ORF66 [125,128-130]. However, ORF 63 is the most frequently expressed gene as it has been detected in humans and in several animal studies and expression of the 2 latency-related VZV genes, ORF 62 and ORF 63, is regulated epigenetically through chromatin structure [125,129]. VZV expresses a unique set of LAT-ORF63 transcripts that are potentially involved in the transition from latency to lytic VZV infection [131,132]. The ability of ORF63 to downregulate ORF62 transcription may play an important role in virus replication and latency [133]. VZV proteins that can be cleaved by granzyme B, including VZV ORF4, and VZV ORF62. However, the possession of a granzyme B cleavage site in VZV proteins was not sufficient to protect against NK cell-mediated cytotoxicity [78].

VZV Glycoproteins

VZV genome contains approximately 74 ORFs of which 11 encode for the following glycoproteins: (1) glycoprotein B (ORF 31) which is critical for entry of virus into cells and association with it enables Siglec-7 to mediate VZV infection; (2) glycoprotein C (ORF 14), the activity of which facilitates the recruitment and subsequent infection of leukocytes and thereby enhances VZV systemic dissemination in humans; (3) glycoprotein E (ORF 68) which binds to a cellular receptor (insulin degrading enzyme) and is essential for VZV infection; (4) glycoprotein H (ORF 37) which is important for cell-to-cell spread of the virus;

(5) glycoprotein I (ORF 67) which facilitates maturation of glycoprotein E; (6) glycoprotein K (ORF 5) that may be important for syncytia formation; (7) glycoprotein L (ORF 60) which is a chaperone for glycoprotein H and is required for the fusion of viral and plasma membranes leading to virus entry into the host cell; (8) glycoprotein M (ORF 50) which is important for efficient cell-to-cell virus spread in cell culture, although it is not essential for virus growth; (9) glycoprotein N (ORF 9A) which presumably directs glycoprotein M to the trans-Golgi network so that these glycoproteins can be incorporated into the virion envelope; and (10) ORF S/L (ORF 0) gene which is required for efficient viral replication and contains an element involved in DNA cleavage [23,134-141].

The following five glycoproteins: glycoprotein K, glycoprotein B, glycoprotein H, glycoprotein L, and glycoprotein E are essential for VZV replication, whereas the remaining five glycoproteins: ORF S/L, glycoprotein N, glycoprotein C, glycoprotein M, and glycoprotein I are dispensable but their absence from the VZV genome does have effects on replication in cell culture and on pathogenesis evaluated in differentiated human tissue [140]. Glycoproteins B and E are major targets of VZV specific CD4+ and CD8+ T-cell reconstitution occurring during HZ after allogeneic HSCT. Hence, VZV glycoproteins B and E might form the basis for novel non-hazardous zoster subunit vaccines suitable for immunocompromised transplant patients [142]. The three VZV glycoproteins: glycoprotein H, glycoprotein L, and glycoprotein C are highly conserved among the alpha herpesviruses. However, unlike VZV glycoproteins H and L which closely resemble their HSV homologs, VZV glycoprotein C exhibits unexpected differences from its counterpart HSV glycoprotein C [143]. VZV glycoprotein C and glycoprotein E have been implicated in membrane attachment, whereas glycoprotein B, glycoprotein H, and glycoprotein L are the necessary components for cell entry where the virion must deliver the capsid through the plasma membrane to initiate infection [140]. VZV glycoprotein L behaves as a chaperone protein to facilitate the maturation of the glycoprotein H protein and the fusogenic activity of the mature glycoprotein H can be abrogated when infected cultures are treated with monoclonal anti-glycoprotein H antibodies [143]. The most well-characterized glycoproteins are those that function in membrane fusion: glycoprotein B, glycoprotein H, and glycoprotein L [140].

Chaperones in VZV Infections

Chaperons are a diverse group of molecular proteins that function during homeostasis and stress conditions such as disease or infection while the core chaperone machinery consists of chaperonins and heat shock proteins (Hsps) [144,145]. Depending on their specific function, molecular chaperones are involved in a plethora of cellular processes by playing key roles in nascent protein chain folding, transport and

quality control [144,145]. The cell protein BAG3, a host chaperon that interacts with VZV ORF 29p, is specifically required for efficient VZV replication and plaque formation [146]. Alteration of host chaperon activity is a novel means of regulating viral replication. Additionally, targeting chaperones may become a new therapeutic modality for treating infections caused by drug resistant herpes viruses [146-148].

VZV replication in cultured cells depends on regulation of the activity of chaperone proteins including Hsp 90 and Hsp 70/Hsc 70 [146,149]. BAG family proteins are regulatory co- chaperones for Hsp 70 [149]. BAG-3 host protein/CAIR-1(the inhibitory co-chaperone) abrogates protein degradation mediated by Hsps [146,149]. In addition to its roles in apoptosis, mitosis, and autophagy, BAG3 has recently been found to drive and modulate several key hallmarks of cancer including: cell adhesion, cellular metabolism, cell cycle progression, metastasis, angiogenesis, enhanced autophagic activity, and apoptosis inhibition [150].

MicroRNAs, Small Non-Coding RNAs, and Circular RNAs of VZV

Most herpesviruses use both host and viral small non-coding RNAs (sncRNA), including microRNA (miRNA), to modulate and regulate lytic as well as latent infections [151,152]. VZV encodes several sncRNAs and miRNAs, and some of these may regulate infection of host cells [151]. sncRNA of VZV are important in modulating gene expression and may have a role in maintenance of VZV latency and/or reactivation [153,154]. As VZV replication is modulated by multiple virally encoded sncRNA, this may help the development of novel anti-sncRNA- based therapies for treatment of VZV infections [153]. Locked-nucleotide antagonists to VZV sncRNA block viral growth and have potential as an anti-viral therapy [152,155]. Some host circular RNAs are deregulated in viral infections suggesting that the virus uses this cellular mechanism to its advantage. However, the fact that members of different viral families are capable of encoding circular RNAs, promises new advances in the scientific understanding of the diagnosis of viral diseases [156]. The identification of VZV circular RNAs in infected cells and tissues belonging to patients with HZ suggests a potential significant role of viral circular RNAs in VZV pathogenesis [157].

Promyelocytic Leukemia Protein

Promyelocytic leukemia protein (PML) is a viral restriction factor inhibiting processes from uncoating to transcription to cell survival [158]. PML cages contribute to the intrinsic antiviral defense by sensing and entrapping VZV nucleocapsids, thereby preventing their nuclear egress and inhibiting formation of infectious virus particles [159]. PML, which has antiviral functions, is an essential organizer of PML subnuclear domains or nuclear bodies (PML-NBs) [160,161]. PML-NBs are membrane less subnuclear domains that are highly dynamic in their protein composition in response to cellular signals [162]. PML-NBs constitute an important mechanism by which IFN control of VZV infection is achieved in vivo and they have been implicated in restricting early herpes viral gene expression [159,160]. PML-NBs are involved in many key cellular processes including: DNA damage response, transcriptional and post-transcriptional regulation of gene expression, apoptosis, cell cycle control, and antiviral defenses [161-164]. VZV pathogenesis in the skin requires ORF61-mediated dispersal of PML-NBs and this modification of host cell nuclear structures depends upon ORF61 SUMO-interacting motifs (SIMs) [160]. More than 50 cellular proteins are known to traffic in and out of PML-NBs, either transiently or constitutively [164]. PML-NBs are implicated in general antiviral defense based on recruiting host restriction factors [165]. Viruses apparently take advantage of several specific PML-NB- associated proteins to promote productive infection [165]. Many viruses including herpesviruses encode proteins or gene products that counteract PML-NB-mediated antiviral defenses by multiple mechanisms [160,161].

SUMOylation, Ubiquitiylation and Small Molecule Inhibitors

SUMOylation which is a type of post-translational modification (PTM) mediated by SUMO-specific proteases: (1) involves covalent conjugation of small ubiquitin-like modifier (SUMO) proteins to the lysine residues of target protein substrates, (2) regulates various important molecular and cellular processes including: transcription, the cell cycle, cell signaling, as well as DNA synthesis and repair, and (3) triggers multiple signaling pathways that are critical for many aspects of cellular physiology [166-170]. SUMOylation is a dynamic and reversible process that regulates protein function at multiple levels and the SUMO substrates are key oncoproteins and tumor suppressors. Additionally, the SUMO machinery components are deregulated at the genomic level in cancer [171]. The well- balanced SUMOylation is essential for normal cellular behaviors, while aberrant SUMOylation or disturbance of SUMOylation is closely related to various diseases such as: cancer, diabetes mellitus, heart failure, neurodegenerative diseases, and cardiovascular diseases [166,167,171]. The delicate balance between SUMOylation and deSUMOylation (SUMO deconjugation) is regulated by sentrin-specific protease (SENP) enzymes possessing SUMO-deconjugation activity [171]. Recently, it became apparent that the repertoire of ubiquitiylation and SUMOylation regulating various biological functions is not restricted to eukaryotic cells, but is also a feature of human viruses, used to extensively exploit complex host-cell networks and homeostasis [172].

Viruses have developed several means, including enhancement of viral macromolecular synthesis and assembly as well as prevention of antiviral immune responses, to regulate diverse cellular pathways in order to create a cellular environment that facilitates viral survival and reproduction [173]. Viruses must engage with the host cell throughout their replication cycles and there are numerous mechanisms by which viruses mediate their effects on the host cell, and this includes targeting various cellular PTMs, including SUMOylation [169,173]. Viruses can manipulate the entire process of SUMOylation through interplay with the SUMO pathway. Conversely, SUMOylation can eliminate viral infection by regulating host antiviral immune components [174]. Given that viruses hijack the biosynthetic and degradative systems of their host, it is not surprising that viruses encode proteins to manipulate the cellular machinery of the host for ubiquitin/SUMO modification at multiple levels [170]. Advanced detection methods and functional studies of ubiquitiylation and SUMOylation during virus-host interplay have revealed that human viruses have evolved a large arsenal of strategies to exploit these specific PTM processes [172]. SUMOylation of host and viral proteins greatly impacts host innate immunity through viral manipulation of the host SUMOylation machinery to promote viral replication and pathogenesis [168].

Members of the several viral families, including herpesviruses, have been shown to modulate SUMOylation [173]. SUMOylation is a modification for successful viral infection across a broad range of viruses including VZV that plays an essential role in the regulation of protein function [168,174]. The interplay between human herpesviruses and the ubiquitylation/SUMOylation modification system has been extensively investigated in the past decade and it was found that infection with some herpesviruses has been linked to many human diseases including cancers [170]. Increased understanding of the many roles of SUMOylation in viral infections can lead to novel insight into the regulation of viral pathogenesis with the potential to uncover new targets for antiviral therapies [168].

The recent progress in the development of inhibitors targeting SUMOylation and deSUMOylation permits evaluation of the therapeutic potential of targeting the SUMO pathway in cancer [171,175]. The recently developed small molecule inhibitors enable therapeutic targeting of the SUMOylation pathway [175]. A number of small molecule inhibitors with different scaffolds and mechanisms of action have been discovered by researchers and the first drug inhibiting SUMO pathway (SUMO E1 inhibitor; TAK-981) has entered to clinical trials for the treatment of cancers [167,171]. Blocking SUMOylation not only leads to reduced cancer cell proliferation but also to an increased antitumor immune response by stimulating IFN signaling, indicating that SUMOylation inhibitors have a dual mode of action that can be employed in the fight against cancer [175].

Hematopoiesis and Bone Marrow Microenvironment

The BM niche or microenvironment has the following two components: (1) cellular components including HSCs in addition to MSCs and their derivatives; and (2) functional components that are composed of growth factors and cytokines which regulate hematopoiesis [9,176-180]. The hematopoietic niche plays a critical role in the daily and circadian production of immune cells from the BM [181]. Different cytokines including: IL- 1β, IL-6, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, macrophage- colony stimulating factor (M-CSF), and granulocyte macrophage (GM)-CSF have been recognized to control the growth and development of HSCs [182]. IFN-γ signaling can affect HSC homeostasis directly by altering gene expression in HSCs and indirectly by altering the regulatory roles of neighboring niche cells [183]. HSCs which give rise to all blood cells are maintained and regulated by special microenvironment or niches in the BM cavity in addition to NOTCH signaling [1177,184]. Distinct stromal or hematopoietic progenitor cells in the BM generate signals that regulate self-renewal, proliferation and trafficking of HSCs [185].

Hematopoiesis, the ability of the BM to generate large amounts of blood cells required on a daily basis, is maintained by the complex interactions between HSCs and MSCs within the BM microenvironment [186-188]. Hematopoiesis, which depends on a highly orchestrated process of proliferation and differentiation of hematopoietic stem and progenitor cells (HSPCs), can be rapidly adapted under stress conditions such as infections to meet the specific cellular needs of the immune response and the ensuing physiological changes [188]. HSC niche supports steady-state hematopoiesis and responds to the changing needs during stress and disease [184]. The molecular processes governing hematopoiesis involve the interplay between lineage-specific transcription factors and a series of epigenetic processes including DNA methylation and covalent histone tail modifications including acetylation, methylation, phosphorylation, SUMOylation and ubiquitylation [189]. The specific effects of acute and chronic viral infections on blood cell production occur at the following four different levels: (1) direct viral infection of HSPCs, (2) viral recognition by HSPCs, (3) indirect effects on HSPCs by inflammatory mediators, and (4) the role of the BM microenvironment on hematopoiesis upon virus infection [188].

Exogenously infused MSCs are thought to migrate to injury sites through peripheral blood stream and participate in tissue repair [190]. Several studies have shown that the numbers of MSCs significantly increase in the peripheral circulation after injuries such as bone fracture, skin injury, and severe burns in addition to chronic diseases such as osteoporosis then MSCs become recruited to the sites of tissue injury [190-194]. Additionally, granulocyte-CSF (G-CSF) can mobilize MSCs from BM into peripheral blood then mobilized MSCs become recruited to the sites of tissue injury to participate in tissue repair and healing [195-197].

Nestin, an intermediate filament protein, was initially reported to be expressed in neuroepithelial stem cells, then nestin expression has been reported in migrating, proliferating and regenerating cells in various body systems and tissues including: brain, spinal cord, BM, heart, lung, and gastrointestinal tract [198,199]. However, several studies have shown a particular association between nestin and functional BM-MSCs. Hence, nestin may characterize a subset of BM perivascular MSCs which contribute to bone development and are closely associated with HSCs [198,200]. Nestin has been reported to enhance stem cell survival after transplantation by inhibiting endoplasmic reticulum (ER) stress-induced apoptosis, improving protection, and repair of the lung inflammatory injury [201]. Some BM-MSCs are nestin-positive and they regulate activation of HSCs [202]. Human olfactory mucosa contains a population of nestin-positive MSCs that secrete chemokine C-X-C motif ligand 12 (CXCL12) and may have promote CNS repair [202]. Nestin + or leptin receptor expressing ($LepR^+$) MSC cells are the major source of stem cell factor (SCF) and CXCL12 in the BM microenvironment and they play a major role in HSC maintenance and hematopoiesis [203,204]. They play a crucial role in the steady-state hematopoiesis process, as well as hematopoietic regeneration and the homing of HSCs after myeloablative injury and/or HSC transplantation [203]. Transplantation of $nestin^+$ BM-MSC can improve cardiac function in an acute myocardial infarction model by recruiting resident cardiac endothelial cells to the infarcted border region via the CXCL12/CXCR4 chemokine pathway [200]. Several studies in humans and in animal models have shown that BM-MSCs, including nestin positive stromal cells, are capable of differentiation into functional pancreatic β-cells and can participate in the control or cure of diabetes mellitus [205-208]. Conversely, nestin + MSCs may play a role in the progression of various diseases [198]. Recent technical advancements such as single-cell and spatially resolved transcriptomics approaches have allowed quantitative spatial analysis of BM cellular components with extraordinary precision [209-211].

Varicella Zoster Virus Vaccines

Prevention of VZV through vaccination is a priority to avoid the

significant burden of the infection and complications in susceptible individuals [212,213]. Currently there are two HZ vaccines that are recommended for use by the advisory committee on immunization practices (ACIP): (1) the live-attenuated vaccine (ZVL: Zostavax, Merck) using vOka strain VZV licensed by the US-FDA in 2006; and (2) the recombinant adjuvanted subunit vaccine (RZV: Shingrix, GlaxoSmithKline) containing recombinant VZV glycoprotein E approved by the US-FDA in 2017 [212,214-216]. The safety and efficacy of both vaccines have been demonstrated in several clinical trials in immunocompetent adults and in selected immunocompromised persons [212,215]. However, the recombinant adjuvanted VZV glycoprotein E subunit vaccine (RZV) is more effective for prevention of HZ than ZVL with higher and more persistent antibody responses and this allows vaccination in severely immunosuppressed patients [215-217]. A systematic review that included 13 studies showed that both RZV and VZL are immunogenic and have an acceptable safety profile in adults and children living with HIV [218]. Another systematic review that included 5 clinical studies [4 RCT and 1 retrospective study] comprising 3048 individuals on the use of 3 different VZV vaccines (RZV, inactivated VZL, or single dose of an Oka strain high-titer zoster-equivalent vaccine) showed that the vaccinated groups of patients demonstrated a significant reduction in the risk of VZV infection among recipients of HSCT, without an increase in adverse events. The systematic review showed the effectiveness and tolerability of VZV vaccines as a preventive measure against HZ for HSCT recipients [219].

Regarding the use of RZV, a systematic review and meta-analysis which included 37 studies indicated that the vaccine elicits robust immunogenicity and overcomes immunocompromising conditions [220]. Also, data from a pilot study that included 38 cancer patients treated with ICIs suggested a strong and long-lasting immunogenicity of RZV in ICI-treated patients [221]. Additionally, several studies have shown that RZV has a clinically acceptable safety profile and elicits robust immune responses in elderly subjects as well as in immunocompromised individuals including heavily pretreated patients with HMs such as MM, non-Hodgkin lymphoma (NHL), and chronic lymphocytic leukemia (CLL) who are at increased risk of HZ and recipients of autologous HSCT [222-225]. A systematic review and meta-analysis that included 7 RCTs on the use of the RZV in: transplant recipients, cancer patients undergoing chemotherapy, individuals with preexisting autoimmune diseases and HIV-infected patients showed that HZ vaccine reduces the risk of HZ infection in immunocompromised individuals and it recommended that the vaccine should be routinely offered to immunocompromised individuals, preferably before chemotherapy or treatment [226]. Even among recipients of allogeneic HCT, RZV has been shown to be safe, and tolerable, without increasing the rates of GVHD [227].

The live attenuated HZ vaccine (Zostavax) has been shown to be safe and effective in reducing the incidence of HZ and postherpetic neuralgia [228-230]. As use of the live- attenuated VZV vaccine was previously contraindicated for immunocompromised individuals, a non-live vaccine or inactivated zoster vaccine (VZI) was developed by inactivation (heat or irradiation) of the live-attenuated VZV vaccine (VZL; Oka/Merck) and this inactivated vaccine was used before RZV was in clinical trials [231,232]. The efficacy of VZI has been demonstrated in patients with solid tumors, HMs, HIV, as well as in recipients of autologous HSCT [231,232]. However, a study showed that the live HZ vaccine is immunogenic and safe when administered 2 years after HSCT [233]. A recent study showed that circulating plasma exosomes from HZ contain proteins conferring a prothrombotic state to recipient cells and can activate platelets leading to the formation of platelet-leukocyte aggregates, leading ultimately to an increase HZ vaccine uptake and a decrease in the risk of stroke in recipients of the vaccine [234].

Oncolytic Viruses and the Future Role of VZV

Viruses have two opposing faces: on one hand they can induce harm, disease as well as complications that may be associated with significant morbidity and mortality and rarely predisposition to cancer; while on the other hand, viruses may provide hope to treat several interactable medical illnesses [235,236]. Specific viruses are useful in certain situations or in the treatment of certain diseases including: use of viruses as vaccines; use of genetically engineered or naturally occurring viruses in oncolytic therapy to treat various cancers; and use of viruses as vectors in: induced pluripotent stem cells (iPSCs), gene therapy for various hereditary and acquired diseases, as well as chimeric antigen receptor (CAR) T-cell therapy [235-243]. Oncolytic viruses (OVs) selectively replicate in and subsequently kill cancer cells and they can spread within the tumor without causing damage to surrounding healthy or normal tissue. Hence, OVs can be used in combination with cytotoxic chemotherapy to have synergistic anticancer effects as they can efficiently destroy cancer stem cells in several cancers [241,244,245].

Alpha-herpesviruses can induce apoptosis, autophagy and necroptosis through different molecular pathways. These pathways influence viral infection and replication and are a potential avenue for treatment of cancer [246]. HSV has the following advantages: (1) quick replication in cells and infection of multiple types of cancer cells, (2) easy modification and insertion of its relatively large genome, (3) prevention by antiviral agents, (4) modification of its glycoprotein can improve targeting of tumor cells, and (5) ability to escape the immune response of the host. These advantages make HSV an efficient OV [247].

GBM, the most aggressive form of malignant brain tumor, carries poor prognosis as it poorly responds to standard therapies such as surgery, radiotherapy, chemotherapy with alkylating agents, and traditional immunotherapy [248-251]. Multiple studies have shown that exposure to VZV, documented by total anti-VZV IgG levels or by self-reported history of chickenpox, has been associated with a lower risk of GBM [252-257]. Recently, few potential alternative therapies have evolved and these include new immunotherapeutic approaches, medications which target specific cellular receptors, and OVs [248,249].

Oncolytic virotherapy utilizes engineered viruses to exert an anti-tumor effect via both direct oncolysis and stimulation of an immune response within the tumor microenvironment [250]. Many OVs have been investigated in completed and ongoing clinical trials and while safety has been demonstrated, clinical outcomes have been variable, often with only a subgroup of patients showing a significant response [250,251]. In patients with GBM, combining OVs with modern

therapeutic approaches may boost the immune response to provide significant benefits and may become a significant area of research aiming to develop the most effective treatment regimens [248,249]. In June 2021, Teserpaturev (Delytact) which is a triple- mutated third-generation oncolytic HSV type 1 received provisional approval for the treatment of GBM in Japan [251,258,259].

VZV vaccines have been shown to induce cytotoxic and proimmunogenic changes in the tumor microenvironment. Hence, these vaccines are potentially promising platforms for intratumoral immunotherapy, either alone or combined with vaccine- or tumor-derived MHC-I-restricted peptide epitopes [260]. OVs can be loaded in various delivery vehicles including stem cells such as MSCs and neural stem cells to enhance the promising therapeutic efficacy against tumor cells. Thus, stem cells act as an emerging delivery vehicle for genetically modified OVs to promote anti-tumor action in tumor cells [261-263]. MSCs exhibit tumor-trophic migration characteristics. Hence, MSCs loaded with OVs can improve delivery of the therapeutic cargo to isolated tumors or the sites of metastatic malignancies [263,264]. Additionally, several studies strongly support the use of human MSCs as safe and effective cell carriers for different types of OVs including oncolytic adenovirus, HSV, measles virus, myxoma virus, and reovirus in order to maximize delivery to the tumor bed and elicit antitumor efficacy [265-267].

Despite indications of potential links between natural VZV infections and the favorable outcomes in diverse cancer types, the oncolytic properties of VZV have not been extensively explored, with the exception of one study which showed that a laboratory strain of VZV engineered with deletion of ORF gene and the addition of IL-12 can be used as a novel VZV-based oncolytic virotherapy [33-37]. Nevertheless, great progress has been achieved in the development of OVs and oncolytic therapy has become a feasible and effective treatment or supplementary method to cure cancer [268].

Conclusions Including Explanations of the Beneficial Effects of VZV

As clearly illustrated in different sections of this review, VZV differs from other herpes viruses in many aspects and it has several peculiar features. The reported beneficial effects of VZV infection in immunocompromised patients are rather outstanding and have translated into improved outcome of primary disease and prolongation of OS. These outcomes should encourage researchers and scientists to give this potentially useful virus the attention it deserves.

As shown in various sections of the review article, the various elements that are implicated in VZV infections are illustrated in Figure 3 [9,23,28,75-77,79,82,111,134,144,151,152,159,160,198,200]. Possible explanations of stimulation of BM function by VZV infections include: (1) VZV infections cause cytokine, chemokine, and growth factor release to stimulate hematopoiesis in the BM; (2) VZV infections cause modulation of the immune system to enhance BM activity; and (3) VZV infections exert direct and indirect effects on hematopoietic as well as stromal cells such as MSCs in BM niche to positively influence the hematopoietic process. In patients having HMs and solid tumors, the positive effects of natural VZV infection or VZV vaccines on the primary malignancies and the survival of patients having these cancers can possibly be explained by the oncolytic as well as the immunological effects of the virus, the VZV vaccines or their constituents.

The positive effects of VZV infection including stimulation of BM function and the possible oncolytic effects of the virus on diseases such as BM failure syndromes, HMs, and even solid tumors can occur through direct and indirect immunological mechanisms and they merit thorough investigations. Explanation of the stimulatory effect of VZV exerted on granulocytic, erythroid and megakaryocytic precursors in the BM that is subsequently translated into increases in WBC count, hemoglobin level and platelet count as well as the antitumor effects of the virus may be explained by one or more of the mechanisms outlined or may be due to a new mechanism that needs to be elucidated.

Since VZV DNA has rarely been isolated from human BM using molecular techniques such as PCR and NGS, the reported positive effect of the virus on BM function can possibly be explained by indirect mechanisms exerted through complicated interactions between various immune and other cells infected by the virus, the cytokines and chemokines stimulated, as well as the signalling pathways involved and subsequently this complicated network will either directly or indirectly affect certain components of the BM microenvironment ultimately leading to stimulation of megakaryocytic, granulocytic and erythroid precursors in the BM.

VZV glycoproteins, other constituents of the virus and VZV vaccines offer promising opportunities for use in oncolytic virotherapy and cancer immunotherapy. The virus itself, modified or engineered versions of the virus or specific constituents such as ORFs, and glycoproteins obtained from the serum of patients infected with VZV or inhibitors of SUMO pathways may ultimately become extremely valuable therapeutic modalities in the management of patients with various BM failure syndromes, HMs, and solid tumors. Apparently, there is limited experience in using VZV or its constituents in oncolytic therapy to treat patients with HMs and solid tumors. Therefore, more attention should be given to this potentially useful virus to explore its potential and future role in treating: BM failure syndromes, HMs, various solid tumors, as well as neurodegenerative disorders.

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