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Review Article

Varicella Zoster Virus Infections in Patients with Hematologic Malignancies and Bone Marrow Failure and in Recipients of Hematopoietic Stem Cell Transplantation

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Abstract

Varicella zoster virus infections can cause can cause serious complications that carry significant morbidity and mortality. The hematological complications of VZV infections can range from transient cytopenias to severe aplastic anemia that may require allogeneic hematopoietic stem cell transplantation. On rare occasions, these infections have been reported to be associated with increased risk of developing lymphoid malignancies and solid tumors. On the contrary, there is growing evidence showing certain beneficial effects of the virus in immunocompromised individuals and these effects may be translated into stimulation of bone marrow function, prolongation of overall survival, and specific antitumor effects.

In this review which gives particular attention to consequences of varicella zoster virus infection in patients with bone marrow failure, hematologic malignancy and recipients of stem cell transplantation, the following aspects of the virus will discussed: epidemiology, pathogenesis, clinical consequences, management of infections; bone marrow microenvironment and stress-induced hematopoiesis; cells implicated in the pathogenesis of the virus such as: mesenchymal stem cells, dendritic cells, natural killer cells, T-cells and mononuclear cells; the involved cellular proteins such as open reading frames, glycoproteins, promyelocytic leukemia protein, chaperons, and SUMOs; extracellular vesicles, exosomes, and micro-RNAs; as well as signaling pathways, cytokines, chemokines, and interferons that are implicated in the pathogenesis of VZV infections.

Keywords: Varicella zoster virus; Bone marrow failure; Hematologic malignancies; Hematopoietic stem cell transplantation; Vaccination; Hematopoiesis; Mesenchymal stem cells; Dendritic cells; Open reading frames; Exosomes; Cytokines; Signaling pathways

Introduction to Varicella Zoster Virus Infections

Varicella Zoster Virus (VZV) is a double stranded DNA virus that belongs to the alpha group of herpes viruses [1-4]. It is a human neurotropic virus, which is highly contagious, and it is an exclusively human pathogen and this makes is extremely difficult to find an animal model for the virus [5-7]. VZV genome, which is the smallest among herpes viruses, has 74 Open Reading Frame (ORF) proteins [1-4]. The genome consists of 2 main coding areas, one long segment and one short segment, each of which is flanked by internal repeat and terminal repeat sequences [2-4]. The virion is composed of an icosahedral nucleocaspid; that harbors the DNA genome; surrounded by a tegument layer, which is covered by a lipid envelope that has glycoprotein spikes [1-4]. During its evolution, the VZV genome has lost almost all the genes that are not essential for its survival [3]. The relatively small genomes and the high proliferation rates allow viruses such as VZV to accumulate mutations that continuously present the host with new challenges. As a consequence, viruses either escape detection or modulate host physiology often by redirecting cellular pathways to their own advantage [8].

Primary VZV infection (chickenpox) occurs in childhood then the virus becomes latent in the nerve ganglia till it becomes reactivated decades later to cause Herpes Zoster (HZ) which is manifested by painful skin eruption with characteristic dermatomal distribution [1,9-12]. Reactivation of VZV is usually predisposed to by immunosuppression due to: old age; diabetes mellitus; chronic obstructive airway disease; end-stage renal disease; Hematologic Malignancies (HMs); solid tumors; autoimmune diseases; immunosuppressive therapies; trauma; cytotoxic chemotherapy; Hematopoietic Stem Cell Transplantation (HSCT), and Solid Organ Transplantation (SOT) [9-12].

Risk Factors and Epidemiology

The risk factors for VZV infections include: (1) old age; (2) hereditary predisposition such as: inborn errors of RNA polymerase III, certain genetic mutations such as: GATA2, DOCK 2, DOCK 8, IFNGR1, and TYK2, as well as genetic variation in the HLA region such as HCP5; (3) Immunodeficiency caused by: HMs such as leukemia, lymphoma, and multiple myeloma; solid tumors; HSCT; SOT; immunosuppressive agents including corticosteroids; cytotoxic chemotherapy; novel therapies and monoclonal antibodies

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such as thalidomide, lenalidomide, bortezomib, rituximab, and alemtuzumab; human immunodeficiency virus; diabetes mellitus; end-stage renal disease; collagen vascular disorders such as systemic lupus erythromatosis; and (4) use of statins, exposure to sunlight or immunotoxins, mechanical trauma, and psychological stress [13-42]. The following 4 geographical genotypes were initially identified: genotype A in Africa and Asia, genotypes B and C in North America and Europe, and genotype J in Japan and South Korea [43,44]. However, the recent use of single-nucleotide polymorphism as well as restriction fragment length polymorphism has allowed identification of the following new VZV genotypes: E1, E2, M1, M2, M3, M4, VI, VII, VIII, and IX in various geographical locations [43-52].

Varicella is an endemic disease in most parts of the world. However, the introduction of vaccination against varicella in many countries has resulted in a substantial decrease in the incidence of chickenpox in young children [53-58]. The epidemiology of VZV infections is usually influenced by the following factors: age, gender, season and climate, geographic location, level of immunity, history of contact with infected individuals, and history of vaccination [54-61]. The following additional factors influence the incidence of VZV infections in patients with HMs, and BM failure and in recipients of HSCT: the type of HM; the cytotoxic chemotherapy, immunotherapy or novel therapy administered; the type of HSCT offered; complications of HSCT particularly GVHD; acyclovir prophylaxis and its duration; as well as CD4+ and CD8+ cell counts [17,62-66].

Pathogenesis of VZV Infections

Primary VZV infection causes viremia in T-lymphocytes and viremia causes the characteristic skin eruption [67,68]. Later on, the virus migrates retrograde into dorsal root ganglia to establish latency. VZV reactivation from dorsal nerve ganglia causes antegrade travel of the virus to induce the dermatomal part of HZ infection [67-69]. VZV is a highly fusogenic virus. Fusion of VZV-infected cells is a consequence of virally expressed glycoproteins and it permits entry of VZ virion into the intracellular cytoplasm [70]. Cell-to-cell fusion induced by VZV infection occurs among fibroblasts and keratinocytes during formation of skin vesicles in both chickenpox and HZ infections [71-78]. In classical human infection, VZV rarely infects dividing cells such as skin fibroblasts, differentiated keratinocytes, mature T-cells, and neurons. However, the virus can productively infect these cells and use their machinery to replicate the viral genome [72]. Both VZV-ORF 28 and VZV-ORF 29 genes are expressed during VZV lytic infection but only the latter is expressed in latently infected neurons [73].

Autophagy, self-eating which involves degradation of cytoplasmic constituents in lysosomes, is closely associated with VZV infection [3,74]. Unlike HSV, VZV genome has no inhibitors of autophagy [3]. VZV-induced autophagy facilitates VZV glycoprotein biosynthesis and processing [69]. During VZV infection autophagy is up-regulated and autophagic flux is increased, while inhibition of autophagy leads to a marked reduction in viral spread. In addition, inhibition or block of autophagic flux may yield higher VZV titers [75]. Modulation of protein acetylation via Histone Deacetylases (HDACs) is a critical regulatory factor during infection by herpes viruses [76]. Viruses have evolved a wide array of mechanisms to destroy HDAC functions [76,77]. Most viruses struggle to utilize the chromatin machinery of host cells to promote efficient lytic infection and to control persistent latent states [78]. Ultimately, epigenetic manipulation using DNA methyl transferase inhibitors and HDAC inhibitors may become novel epigenetic antiviral therapies [79].

Clinical Manifestations and Complications of VZV Infections

The clinical manifestations and complications of VZV infections include: (1) prodromal symptoms such as fever, malaise and local pain; (2) typical skin eruptions: vesicular eruption that spares limbs and mainly involves the face, head and trunk in chickenpox; while in HZ: the crops of skin lesions involve at least 1 dermatome, they are usually unilateral and commonly appear over chest, then trigeminal nerve distribution, and they may progress from papules to vesicles the crusts; (3) lung involvement in the form of pneumonia which is particularly severe in adults; (4) nervous system complications include: postherpetic neuralgia; meningitis, cerebritis and encephalitis; vasculopathy: headache, fever, mental changes, transient ischemic attacks, and stroke; segmental weakness and radiculopathy; myelitis and myelopathy: progressive myelitis and spastic paraparesis; cranial neuropathies and giant cell arteritis; Guillain-Barre syndrome; and Ramsay Hunt syndrome; (5) eye manifestations include: acute retinal necrosis (ARN) and progressive outer retinal necrosis; scleritis; keratitis, cataract, corneal ulcers, scars and perforation; proptosis and exophthalmos; optic neuritis, optic atrophy, and papilledema; ophthalmoplegia: diplopia and ptosis (III, IV and VI cranial nerves); posterior uveitis, retinal detachment and blindness; (6) BM suppression and secondary malignancies; and (7) other complications: secondary bacterial infection of skin lesions; enteric complications;visceral and disseminated infection; osteonecrosis and spontaneous exfoliation of teeth; and radicular pain without skin rash (zoster sine herpete) [5,9,22,30,80-97].

However, in severely immunocompromised individuals: atypical skin eruptions and disseminated infection in the absence of skin lesions may occur because pre-existing antibody does not prevent VZV reactivation, but may contribute to decreased viral load thus resulting in mild clinical course . In this group of patients, mortality rates range between: 5% and 15% [22,98].

BM suppression and cancers associated with viral infections and VZV

Peripheral blood cytopenia is the hematological hallmark of septic shock [99]. In addition, viruses can have tremendous impact on the hematopoietic process and the consequences of viral infections on the BM include: aplastic anemia, variable cytopenias, hemophagocytic lymphohistiocytosis, lymphoproliferative diseases, and a variety of other cancers [87,88,100,101]. Examples of the viruses that can have adverse effects on BM function are: Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), VZV, Herpes Simplex Virus (HSV), Parvovirus B-19, Human Immunodeficiency Virus (HIV), hepatitis A and C viruses, and dengue virus [9,87-89]. The mechanisms involved in the adverse consequences of viral infections on the BM include: direct viral infection of HSPCs, viral recognition of HSPCs, indirect effect on HSPCs induced by inflammatory mediators, and the role of BM microenvironment on hematopoiesis induced by viral infection [87,102-105]. VZV infections have been reported to cause: transient pancytopenia, aplastic anemia that may require allogeneic HSCT,

and an increased risk of developing solid tumors as well as lymphoid malignancies [30,87,90-97].

Laboratory Diagnosis of VZV Infections

The diagnosis of VZV infection is usually made on clinical grounds based on the presence of the characteristic skin eruptions of chickenpox or HZ [3,68,106]. To confirm the diagnosis of VZV infection, the following additional diagnostic techniques may be needed: (1) virus isolation by culture which carries a low yield rate; (2) serology using Enzyme-Linked Immunosorbent Assay (ELISA); (3) direct fluorescent antibodies on scrapings obtained from active skin lesions; and (4) real-time polymerase chain reaction (RT-PCR) which has higher sensitivity than serological assays [3,68,106].

Acyclovir resistance of VZV infections has been reported on rare occasions in immunocompromised individuals. Drug resistance can be determined by genetic testing [107-109]. Ultra-deep sequencing, after initial detection of drug resistant mutations by Sanger sequencing, can be used in immunocompromised hosts [110].

Treatment, Vaccination and Antiviral Prophylaxis

Treatment of VZV infections

The available therapies for VZV infections include acyclovir, which has been the standard of care for long time; valaciclovir; famciclovir; bromovinyl deoxyuridine or brivudine; and Bicyclic Pyrimidine Nucleotide Analogues (BCNAs) [9,111-114]. In immunocompromised individuals, it is recommended to administer high-dose acyclovir Intravenously (IV) for a total duration of 7 to 10 days [9,13,113,114]. Brincidofovir can be used in the treatment of acyclovir-resistant disseminated VZV infection in immunocompromised patients such as recipients of HSCT having GVHD [115]. In addition, IV and intravitreal foscarnet can be used in the treatment of acyclovir-resistant Acute Retinal Necrosis (ARN) caused by VZV infections [116-118]. BCNAs are not active against VZV strains that are resistant to acyclovir or brivudine and that bear mutations in the viral thymidine kinase gene. Hence, they are more potent against clinical isolates of VZV than acyclovir or brivudine [112].

The other new therapeutic agents for the treatment of VZV infections include: (1) the novel anti-VZV compound (35 B2 derivative of pyrazolo-1,3,5-triazin-4-one) can inhibit both acyclovir-resistant and acyclovir-sensitive strains of VZV by targeting herpes virus major capsid protein and inhibiting normal capsid formation; (2) aryl bicyclic nucleoside analogues such as FV-100; (3) BCNAs as various types of these agents have been found to be promising future therapies for VZV infections; and (4) bicyclic aryl furano pyrimidines [111,118-123]. For Post-Herpetic Neuralgia (PHN), gabapentin as well as local and systemic analgesics are usually prescribed [113,124-126].

VZV vaccines

There are two types of VZV vaccines: (1) varicella vaccines such as varilrix, varivax, and the combined measles, mumps and rubella and varicella vaccine, all of which contain live-attenuated oka strain of VZV; and (2) HZ vaccines that include zostavax, and HZ/su [69,127,128]. Zostavax contains the live attenuated VZV oka strain and it is given as one injection subcutaneously. It has overall efficacy of 51.3% and it reduces the incidence of HZ by 51% within a 3 year period [69,127,128]. HZ/su is a subunit vaccine candidate that has recently shown improved efficacy in prevention of HZ in 2 phase III clinical trials. It is non-live, recombinant subunit glycoprotein E combined with adjuvant ASO1. It is given intramuscularly twice and it is recommended for immunocompetent individual's ≥ 50 years with overall efficacy of 97.2% [69,127,128]. Post exposure immunoglobulin prophylaxis with ZariZIG is usually administered to individuals having recent contact with patients having active VZV infections [127,129].

The main indications of VZV vaccination include: post-exposure prophylaxis, individuals ≥ 50 years of age, and health care providers [6,128,129]. VZV vaccination is traditionally contraindicated in the following groups of patients: patients having HMs and solid tumors particularly those receiving cytotoxic chemotherapy or novel agents; recipients of HSCT or SOT receiving immunosuppressive therapies; patients having autoimmune treated monoclonal antibodies; patients with acquired immunodeficiency syndrome; patients receiving long-term corticosteroid therapy; and individuals having active VZV infections [6,129,130].

Despite the rare reports of breakthrough VZV infections that may become disseminated and life-threatening particularly in immunocompromised hosts, VZV vaccines including the live-attenuated ones are generally safe and effective even in immunocompromised individuals such as: recipients of HSCT and SOT; patients with HMs and solid tumors; patients with diabetes mellitus, autoimmune disorders and renal disease; elderly individuals; patients receiving corticosteroid maintenance therapy; and individuals with history of HZ infection [129,131-148].

Prophylaxis against reactivation of VZV infections

Reactivation of VZV infections may be encountered in patients with various HMs and in recipients of autologous as well as allogeneic HSCT [41,64,149-151]. Reactivation of VZV infections in these immunocompromised patients may be associated with serious complications such as disseminated infections that carry significant morbidity. Additionally, mortality rates may reach 34% [41,64,66,149-152]. Therefore, in order to prevent complications of VZV infections in these patients, prevention of reactivation of VZV infections particularly in patients with with MM, low lymphocytic count, and those on long-term corticosteroid therapy is needed [41,64,66,149-153]. Consequently, acyclovir prophylaxis is recommended in patients with HMs receiving intensive chemotherapy or novel agents, and in recipients of autologous as well as allogeneic HSCT [64-66,149-151,154].

Initially, the trend was to give acyclovir prophylaxis for up to 6 or 12 months in recipients of autologous and allogeneic HSCT respectively [64,65,152,153]. Nowadays, the recent literature is in favor of administering acyclovir as antiviral prophylaxis for periods of time longer than one year in HSCT recipients [64,65,149,151-153]. Several retrospective studies have shown that extended acyclovir prophylaxis has been shown not only safe but also effective [149,153]. However, the benefits and safety of long-term prophylaxis with low-dose acyclovir should be confirmed in large prospective trials, as long-term use of acyclovir may be associated with side effects as well

as evolution of drug resistance [65,153].

The Reported Beneficial Effects of Varicella Zoster Virus

VZV behaves differently from other herpes viruses as it differs from them in many aspects [1-4,9,70]. Recently, there has been growing evidence on the beneficial effects of the virus in immunocompromised hosts and these effects are translated into prolongation of Overall Survival (OS) [9,155]. The reported beneficial effects of the virus include: stimulation of bone marrow activity in patients with HMs and Bone Marrow (BM) failure syndromes, antitumor effects in various HMs and solid tumors, and association with Graft Versus Host Disease (GHVD) which has anticancer effects [9,13,156-161].

The positive effects of VZV on BM function and HMs

In a single center, retrospective case-controlled study that included 16 episodes of Varicella Zoster Virus (VZV) infection occurring in 14 patients with various types of HMs and BM failure syndromes subjected to various forms of immunosuppressive therapies, cytotoxic chemotherapy and HSCT, Al-Anazi K.A. et al reported an increase in white blood cell count, Hemoglobin (Hb) level, and Platelet (PLT) count starting approximately 6 weeks following VZV infection [9]. This stimulation of the 3 hematopoietic cell lines in the BM caused by VZV infections lasted for periods longer than 3 years post-VZV infection. The study showed that VZV could behave differently from other members of the herpes group of viruses such as CMV and EBV and that VZV infection might cause stimulation of BM function starting 6 weeks following VZV infection and lasting for several years thereafter [9]. Al-Anazi KA. et al., postulated that immunological changes induced by VZV infection such as cytokine release could account for the stimulation of BM activity encountered following VZV infections [9].

In another single center retrospective study that included 191 patients with Multiple Myeloma (MM) treated initially 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 HSCT and that VZV infections were encountered more frequently in patients with advanced stage of the disease, renal failure and relapsing MM [155]. Despite encountering VZV infections in patients with worse expected prognosis, the OS in patients who developed VZV infection was superior to that in patients who never developed the infection. There was no delay in neutrophil engraftment post-HSCT in patients infected with VZV and engraftment of PLTs occurred earlier in patients infected with VZV [155].

Recently, Al-Anazi K.A. et al reported reversal of Pure Red Cell Aplasia (PRCA) by VZV infection [13]. 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 [13]. Six weeks after the VZV infection, Hb level started to increase gradually and the steady increase in Hb level continued until it plateaued about 14 months following the VZV infection. A repeat BM biopsy showed resolution of the severe erythroid hypoplasia and regeneration of the erythroid precursors in the BM [13].

GVHD and its association with VZV

Immunosuppressive therapies, given to control GVHD, are associated with increased risk of infectious complications [10]. On the contrary, bacterial and viral infections can theoretically contribute to the elevation of inflammatory cytokines after allogeneic HSCT, ultimately leading to aggravation of acute GVHD [11,12]. Interestingly, several studies have demonstrated that VZV infection may trigger chronic GVHD following allogeneic HSCT [156-158]. GVHD is usually associated with graft versus tumor, leukemia or lymphoma, (GVT) effects and provided GVHD is of low-grade, it can translate into improvement in OS in patients with acute leukemia or lymphoma [162-164].

Oncolytic viruses and the rising role of VZV

Viruses can induce harm and disease with early and late complications that may be associated with significant morbidity and mortality in addition to the rare event of cellular transformation and evolution of cancer. On the other side, viruses may provide hope to effectively treat several serious medical illnesses [165,166]. Examples of the usefulness of certain viruses in the treatment of specific diseases include: use of viruses as vaccines; use of genetically engineered or naturally occurring viruses as anticancer agents in the setting of oncolytic virus therapy; use of viruses as vectors in: induced Pluripotent Stem Cells (iPSCs), gene therapy for various hereditary and acquired diseases, as well as CAR T-cell therapy [165-173].

Studies have shown that VZV is the only virus with consistent inverse association with glioma suggesting a protective effect of VZV against glioma [159-161]. Studies have also shown that: the protective effect of prior VZV against the tumor is stronger for high-grade disease glioma and this effect may be mediated by the VZV-specific T-lymphocytes; VZV exhibits an extrinsic oncolytic potential in malignant glioma cultures, thus making it a possible novel candidate for virotherapy in glioblastoma multiforme; and human MSCs are suitable for delivering VZV to the sites of tumor growth [159,160,174]. However, efficacy of oncolytic virotherapy in malignant glioma has the certain difficulties that need to be overcome [174].

Animal and Other Experimental Models for VZV

VZV is an exclusively human pathogen. Hence, VZV pathogenesis, latency, and reactivation are difficult to study [128,175,176]. Due to the cell-associated nature of the virus and the strict host-specificity of infection, our knowledge of host-pathogen interaction and VZV pathogenesis, latency and reactivation remains incomplete [128,175,177]. Development of more efficacious vaccines and antiviral therapies against VZV and better understanding of the host response to VZV infection are hampered by the scarcity of animal models that recapitulate all aspects of VZV infections in humans [128,175-178].

The following animal models have been used but with limited success: (1) guinea pig; (2) cotton rat; (3) Simian Varicella Virus (SVV) in Non-Human Primates (NHPs); and (4) the severe combined immunodeficiency-humanized mouse model [128,177,179-182].

Recently, the following have been utilized to study the pathogenesis of VZV infections: normal human neuronal progenitor cells in tissue-like assemblies; terminally differentiated neurons; and sensory neurons generated from human iPSCs and human Embryonic Stem Cells (ESCs) [175,183-189]. Thus, numerous efforts have been made to develop adequate animal models of VZV infection with limited success because all aspects of VZV infection, latency and reactivation, as well as understanding VZV pathology will remain not only difficult but also incomplete without a suitable model [128,176].

Bone Marrow Microenvironment and Hematopoiesis

The BM microenvironment is the domicile of Hematopoietic Stem Cells (HSCs) as well as the malignant processes that develop in the BM [189]. The BM niche or microenvironment has 2 main components: (1) cellular components such as MSCs, HSCs, and their derivatives; and (2) functional components that are composed of several growth factors and cytokines which regulate hematopoiesis [190-194]. The interaction between the niche constituents and HSCs maintain hematopoiesis [195]. HSCs which give rise to all blood cells are maintained and regulated by special microenvironment or niches in the BM cavity [196]. NOTCH signaling is crucial for HSC maintenance [191]. Distinct stromal or hematopoietic progenitor cells in the BM generate signals that regulate self-renewal, proliferation and trafficking of HSCs [197]. HSC niche supports steady-state hematopoiesis and responds to the changing needs during stress and disease [196]. The nervous system is an important regulator of HSC niche and it influences the development of stem cells [196]. Neural crest-derived MSCs have regulatory pathways that control hematopoiesis in the hematopoietic niche [198,199]. Dysregulation between neural and hematopoietic systems can contribute to disease [196].

Hematopoiesis is the process by which all mature blood cells are produced from stem cells to replace the cells that have completed their lifespan [191,198]. Hematopoiesis, a dynamic biological process that can be influenced by environmental factors such as infection or inflammation, is under tight control of a group of hematopoietic cytokines [200,201]. However, the same cytokines control basal as well as emergency hematopoietic cell proliferation [199]. Pro-inflammatory cytokines are fundamental regulators of hematopoiesis. However, there are differences in the roles of certain cytokines during fetal life and adulthood [202,203]. The different cytokines, chemokines, ligands, and signaling pathways that are involved in hematopoiesis, Hematopoietic Stem And Progenitor Cell (HSPC) proliferation and myeloid differentiation include: (1) cytokines, chemokines, interferons, and growth factors such as:interleukins (ILs): IL-1α, IL-1β, IL-3, Il-6, IL-18, IL-33; Interferons (IFNs): IFN- α, IFN-γ; tumor necrosis factor-α; colony stimulating factors; transforming growth factor-β; fibroblast growth factor; thrombopoietin; angiopoietin; lipopolysaccharide; and prostaglandin E2; (2) ligands such as: Flt3, FMS-tyrosine kinase 3, and Toll-like receptors (TLRs); and (3) signaling pathways such as: NF-κβ, STAT3, and Wnt [200,203,204].

During pathogen exposure, hematopoiesis may yield a progeny in proportions that are different from those produced under steady-state hematopoiesis [201,202,205]. In acute inflammation, IFNs, TNF, and lipopolysaccharide directly stimulate HSC proliferation and differentiation while in chronic inflammation, cytokine-signaling leads to HSC exhaustion and may cause evolution HMs [206]. Cytokines and ligands, which are produced during stress conditions such as infection, include: (1) IFNs; (2) TNF; (3) cytokines such as; Il-1α, IL-1β, IL-3, Il-6, IL-18, IL-23, mtDNA, HMGB1, SCF, and thrombopoietin; and (4) Flt-3 ligand [99,205,206]. However, certain cytokines that are produced during stress conditions have significant effects on HSCs in the BM [206].

The types of BM microenvironment responses to microbial products include: (1) emergency granulopoiesis caused by rapid mobilization of granulocytes and HSPCs from the BM to the peripheral tissues giving rise to short-lived cells such as neutrophils, basophils and eosinophils; (2) suppression or enhancement of erythropoiesis; (3) proliferation and differentiation of HSCs induced by type I IFNs; (4) enhanced output of innate immune cells; and (5) development of extramedullary hematopoiesis to compensate for the diminished BM hematopoietic progenitor cells during infection [100,206]. Pathogens disturb hematopoiesis through direct effect on HSCs by infection or microbial products; and indirect effects on the BM microenvironment [201]. Acute microbial infection elicits profound changes in hematopoiesis with alterations in the proportions of uncommitted progenitor cells. For example, sepsis is characterized by hyperactivity of the immune system manifested by overproduction of pro-inflammatory cytokines and chemokines followed by hypoactivity and neutropenia [201]. However, overproduction of pro-inflammatory cytokines due to chronic inflammation often causes hematopietic failure [201].

Cells Involved the Pathogenesis of VZV

Mesenchymal stem cells

MSCs are adult, non-hematopoietic, multipotent stromal progenitor cells that have the capacity of multi-lineage differentiation and self-renewal [207-212]. They can be isolated from BM, peripheral blood, umbilical cord blood, amniotic fluid, as well as adipose tissue. In addition, they have certain distinguishing features including the characteristic surface markers and they have immunomodulatory and immunosuppressive properties that enable them to have several therapeutic and clinical applications [207-209]. MSCs are major constituents of HSC niche and the BM microenvironment [195]. MSCs are the masters of survival and clonality as they interact with diverse immune cells and different cellular components of the BM microenvironment including normal cells, leukemic stem cells, and progenitor cells [210-213].

The emerging roles of BM-MSCs in host defense include production of cytokines, chemokines and Extracellular Matrix (ECM) proteins to support HSC survival and engraftment, augmentation of antimicrobial responses, and amelioration of injury caused by the host defense to the pathogen [209,212]. BM-MSCs function as a critical fulcrum providing balance by: promoting pathogen clearance during the initial inflammatory response, and suppressing inflammation to preserve host integrity and facilitate tissue repair [212]. MSCs, particularly placenta-derived MSCs and fetal membrane-derived MSCs, are highly susceptible to herpes viruses including VZV [209,214].

In cancer, MSCs are a double-edged sword as they can: exert stimulatory effects on tumor development and have inhibitory effects on cancer cell growth and metastases [215]. MSCs have the following anticancer properties: (1) they can be engineered or modified to become carriers of suicide genes; (2) they can be employed as carriers of anti-angiogenesis factors; (3) cytokine gene expression can be induced in MSCs; and (4) engineered MSCs can be utilized to target cancer stem cells [216-218]. Studies have shown that several types of stem cells including BM-MSCs and NSCs can cross the BBB and reach tumors localized in the brain such as glioblastoma multiforme. Hence, MSCs can be utilized as means of cellular carriers to deliver cytotoxic genes or therapeutic agents for brain tumors [219-223].

Dendritic cells

DCs are BM-derived cells that are located in most tissues including the skin, blood, lymph and mucosal surfaces and form an essential interface between the innate sensing of pathogens and the activation of adaptive immunity [224,225]. They are potent antigen presenting cells that are critical in the initiation of successful primary antiviral immune responses to control and/or eliminate viral infections [225-229]. Functions of DCs include inhibition and control of immune responses as well as bridging the innate and adaptive immune systems [224,229].

DCs use different pathways to present antigens to CD8 and CD4 T-cells [228]. Mature DCs are permissive for VZV infection and DC infection can lead to transmission of the virus to T-lymphocytes in preparation for subsequent dissemination of the virus in the human body to cause disease [225,226].

Natural killer cells

NK cells develop from common progenitors and differentiate from HSCs in the BM and their sources include: BM, peripheral blood, cryopreserved umbilical cord blood, human ESCs, iPSCs, in addition to various cell lines [230-232]. Human NK cells, the third population of lymphoid cells, represent the first line of defense against infections and tumors and they express specific surface markers, intracellular signaling molecules, and transcription factors [232-238]. Recently, it has been shown that NK cells exhibit many of the features associated with adaptive immunity including: generation of long-lasting memory cells, the ability to mount an enhanced secondary recall response to rechallenge, and having distinct gene regulatory functions [236,239].

NK cells play a major role in the immune response to certain malignancies by several mechanisms [236,237,240-243]. They play key roles in innate and adaptive responses through unique NK cell activation mechanisms during early host defense against viruses and tumors [231,236,241]. NK cells are attractive candidates for adoptive cellular therapy in: acute leukemia and solid tumors with either CAR-engineered NK cells or combining NK cells with CD-16 binding antibodies or immune engagers; and allogeneic HSCT to protect against disease relapse by enhancing Graft Versus Leukemia (GVL) effect without causing GVHD [230,232,233,243-247].

NK cells play a major role in the immune response to certain viral infections by direct cytolysis or killing of virus-infected cells to rapidly control viral infection, and secretion of potent immune mediators such as IFN-γ and other cytokines [236,248-250]. NK cells can produce persistent memory in response to certain viral infections and they have multiple mechanisms to kill virus-infected cells through the engagement of extracellular death receptors, and through exocytosis of cytotoxic granules [238,239]. Productive VZV infection actively manipulates the phenotype of NK cells which have a potential role in VZV pathogenesis as they are implicated in controlling infections caused by VZV [251].

T-lymphocytes

It is well recognized that T-cell mediated immunity consists of CD4 and CD 8 effector and memory T-cells and that administration of varicella vaccine generates VZV-specific humoral and cellular immune responses [252]. VZV-specific T-cells and T-cell mediated immunity, which decrease with immunosuppression and advancing age, are essential for controlling VZV infections [252-255].

Infection with VZV induces cellular immunity that protects against reinfection and reactivation of the virus from the sites of latency [256]. CD4+ cytotoxic T-cells are essential in primary host response to acute varicella [257]. Live-attenuated varicella vaccines can induce VZV-specific memory cytotoxic T-cell responses comparable to those occurring in individuals with natural immunity [257]. VZV vaccination increases the magnitude of VZV-specific CD4+ T-cell responses [258]. So, the efficacy of VZV vaccines may be enhanced by eliciting robust CD4+ T-cell responses [259]. In recipients of T-cell depleted stem cell allografts VZV-specific T-cell immunity, which is essential to prevent VZV reactivation, can recover efficiently [260]. In recipients of HSCT: recognition of protective VZV-specific T-cell mediated immunity does not require disease development, and monitoring of VZV-specific cell-mediated immunity can guide antiviral prophylaxis [261].

Mononuclear cells

VZV productively infects human Peripheral Blood Mononuclear Cells (PBMNCs) and monocyte derived macrophages. It induces an IFN-mediated Th1 reaction in PBMNCs and the infected PBMNCs then disseminate the virus to distal organs to produce clinical disease [262-267]. However, growth of VZV in human adult monocytes is incomplete and restriction of VZV growth by monocytes may play a role in defense against VZV infection [268]. In patients with VZV infection, VZV-DNA can be detected in human PBMNCs: (1) by RT-PCR during viremia and within 1-23 days after onset of the skin lesions, and (2) by in situ hybridization for 2-56 days after appearance of the skin eruption [265,266,269].

TLRs, the key components of the host innate recognition system, play a role in the inflammatory cytokine production by monocytes during VZV infection [266]. VZV specifically induces IL-6 in human monocytes via TLR2-dependent activation of the NK-κβ signaling pathway. Additionally, the cytokine response to VZV is species specific [266].

VZV Proteins, Cell Components and Cellular Processes

Open reading frames

Although approximately 80 proteins have been described to be produced in association with VZV infections: 74 ORFs, 3 glycoproteins, 3 IE proteins, only 44 of these ORF genes are essential

for viral replication [2,4,71,269-272]. Also, VZV contains 5 unique ORF genes and it lacks 15 ORF genes that are expressed by HSV-1 [48]. However, the most common ORFs are: ORF 1, ORF 2, ORF 4, ORF 10, ORF 13, ORF 21, ORF 23, ORF 29, ORF 32, ORF 47p, ORF 54, ORF 57, ORF 61, ORF 62, and ORF 63 [2,4,71,270-272].

One complete cycle of VZV replication takes 9-12 hours and leads to a new generation of infectious VZV particles [71]. The expression of the 2 latency-related VZV genes, ORF 62 and ORF 63, is epigenetically regulated [273,274]. ORF 63 is a prominent gene product in productive VZV infection and has critical roles in latent infection and in VZV pathogenesis by aiding neuron and keratinocyte survival [274-276]. Expression of ORF 61 and ORF 62 occurs less than one hour after VZV infection of human fibroblasts [71].

ORF 21 is the first gene product expressed during latency [277]. ORF 7 is a novel VZV skin-tropic factor, which is essential for viral replication [278]. ORF 25 gene product is essential for protein interactions and VZV replication [279]. ORF 54 deletion mutant represents the first VZV encapsidation mutant that can serve as a platform for the isolation of portal mutants via recombination-mediated genetic engineering and can provide a strategy for more studies on VZV portal structure and function [271]. VZV-ORF 47 is critical for replication of the virus in immature DCs and for spread of virus to other cells [228]. The protein coded by ORF 9, ORF 9p, is essential for viral replication by binding to cellular adaptor protein complex 1 [272,280].

Glycoproteins

The lipid envelope of VZV contains numerous glycoproteins that are needed for viral replication and pathogenesis [281]. VZV glycoprotein C activity facilitates the recruitment and subsequent infection of leukocytes, and enhances VZV systemic dissemination in humans [273]. Glycoproteins B and E, the major targets of VZV-specific CD4+ and CD8+ T-cell reconstitution that occurs during VZV infection or reactivation following allogeneic HSCT, might form the basis for novel non-hazardous subunit vaccines suitable for immunocompromised hosts [270]. VZV glycoprotein M is essential for efficient cell to cell virus spread but not for virus growth [282].

Promyelocytic leukemia protein

The cellular protein, Promyelocytic Leukemia Protein (PML), has been identified recently [283,284]. Human PML protein is located on chromosome 15 and has 9 exons and ≥ 11 isoforms [285]. PML is an essential regulator of somatic cell programming and stem cell pluripotency and has diverse functions that regulate response to DNA damage, apoptosis, senescence, and angiogenesis [286-288]. It is a regulator of metabolic pathways in stem cell compartments and it has provided new strategies for controlling stem cell maintenance and differentiation [287]. For its action, PML recruits other proteins such as Sp100, Daxx, Small Ubiquitin-Like Modifier (SUMO)-1, and P53 [288].

Recently, there is a growing body of evidence supporting the impression that PML is a key regulator of cytokine signaling [289]. In addition, PML is involved in: cell death, senescence and antiviral defense and it is able to interact with various partners in the cell cytoplasm or in the nucleus [289]. PML, an IFN-inducible protein that is involved in restricting VZV replication, is a key organizer of large numbers of proteins that are able to be SUMOylated [285,290].

Chaperons

Chaperons are a diverse group of molecular proteins that function during homeostasis and stress conditions such as disease or infection [291]. Chaperons play critical roles in folding and refolding of protein chains, protein transport and translocation through membranes, degradation of proteins, and host-pathogen interaction during infection, and protein quality control [291,292]. ELISA-based tests, which are used to measure the plasma levels of chaperons, give information about the quantity or amount but not the function or activity of chaperons [291]. Molecular chaperons are required for the folding processes of many proteins and the core chaperone machinery consists of chaperonins and heat shock proteins [293]. The cell protein BAG3, a host chaperon, is specifically required for efficient replication of VZV [294]. Alteration of host chaperon activity is a novel means of regulating viral replication and targeting chaperones may become a new therapeutic modality for treating infections caused by drug resistant herpes viruses [294-296].

SUMO proteins and SUMOylation

Post-Translational Modification (PTM) of proteins allows cells to respond to internal and external stimuli [297]. The most studied protein modifications are: ubiquitination, phosphorylation, acetylation, methylation, and glycosylation [297]. PTMs contribute to gene regulation, epigenetics, differentiation, protein degradation, and tumorigenesis [298]. Since the first description SUMOylation in the year 1996, 4 SUMO isoforms have been characterized in humans [296,299,300]. SUMO proteins are essential for the normal function of all eukaryotic cells [301,302]. SUMOylation, a highly conserved and reversible PTM, is manipulated by viruses in order to modulate anti-viral responses, viral replication and viral pathogenesis [297-301]. SUMOylation, a major regulator of protein function that plays an important role in a wide range of cellular processes, is carried out by a cascade of several enzymatic steps where SUMOs are implicated in the regulation of diverse cellular processes [297,300,301,303]. SUMOylation is an important mechanism regulating the activities of various proteins involved in: DNA replication and repair, chromosome packing and dynamics, genome integrity, nuclear transport, signal transduction, and cell proliferation [304].

SUMO-specific proteases are required for the maturation of SUMO precursors and the reversal of a wide range of cellular processes [297,298]. SUMO Ubc9 enzyme represents not only a leading target for viral proteins but also an attractive biomarker in the treatment of most viral-induced human pathologies [299]. VZV-ORF 61p, which appears to target substrates for potential degradation in a SUMO-independent manner, is important in the infectivity of the viral DNA and it has much stronger affinity for SUMO-1 than SUMO-2 and SUMO-3 [298,300,302]. VZV-ORF 29 gene can be ubiquitinated and SUMOylated [305]. Tripartite motif proteins have been implicated in multiple cellular functions including antiviral activity and they rely mainly on their function as E3-ubiquitin ligases [302,306]. Identification and knowledge of virus-mediated PTM manipulation by viral analogs infiltrating ubiquitin/SUMo pathways will help in the development of future antiviral drugs and novel immunotherapies [297-299]. Thus, targeting SUMOs could represent a new therapeutic strategy against viral infections [307].

microRNAs

Micro-RNAs (miRNAs) have several functions that include regulation or modulation of gene expression; downregulation of target protein expression in cells; regulation and maintenance of numerous cellular physiological functions or processes; regulation of interaction between hosts and viruses; and inhibition of viral replication [308-311]. VZV encodes several miRNAs that regulate VZV infection in host cells [310]. The following circulating miRNAs have been detected in patients with VZV infection: miR-197; miR-629; miR-363; miR-132; miR-122; miR-1906; miR-571; miR-1276; miR-1303; miR-943; and miR-661. Hence, these circulating miRNAs can be potentially used as biomarkers of active or latent VZV infection [309,312].

Extracellular Vesicles and Exosomes

Extracellular Vesicles (ECVs), nano-sized cell-derived particles that are released by most cell types, are potent vehicles of intercellular communication to transmit biological signals between cells and are characterized by a specific set of proteins, lipids and nucleic acids [313-316]. ECVs, which were initially considered as mostly cellular debris, are the key mediators of intercellular communication and they can be isolated from various biological fluids including blood, urine, cerebrospinal fluid, amniotic fluid, seminal fluid, and breast milk [313,315,316]. The 4 main types of ECVs are: exosomes, macrovesicles, apoptotic bodies, and oncosomes [313,315,317]. During viral infection, ECVs transport viral genomes into target cells, and intervene in cell physiology to facilitate viral infection [315]. MSC-derived ECVs may provide a new therapeutic option in: cell transplantation or gene therapy for different diseases particularly HMs and in immune regulation, tumor inhibition, and regenerative medicine [313].

Exosomes mediate intercellular communication through functional or biologically active proteins, lipids, and RNAs and they are implicated in normal physiological processes such as modulation of the immune system, metabolism, and neural development; and progression of several pathologies such as cancer, infection and neurodegeneration [316,318]. Exosomes are crucial components in the pathogenesis of viral infections [318]. Viruses including herpes viruses can manipulate exosomal pathways and VZV could utilize the alterations in host exosomes to: enhance spread of the virus, evade host immune surveillance, and elicit pathological effects within the host [319,320]. Exosomes are becoming critical mediators of viral infection-associated intercellular communication and microenvironment alterations [317]. They can be used as: biomarker of disease, and target for therapy in order to control or even eradicate viral infection and they can help to enhance immune responses of the host against pathogens by activating antiviral mechanisms. Thus, exosomes can be used as therapeutic agents to modulate immune responses [317-319].

Role of Cytokines in VZV Infections

Cytokines; that include chemokines, lymphokines, IFNs, ILs, and TNF; are low molecular weight extracellular polypeptides or glycoproteins that are synthetized by different immune cells such as T-cells, neutrophils and macrophages in response to infection, inflammation or trauma [321]. Cytokines are important mediators of immune response and they play an essential role in the expression of cell mediated immunity [321,322].

On the first infection with VZV, induction of CD4 and CD8 T-cells is followed up by generation of VZV IgM, IgG, and IgA antibodies, while memory immunity to VZV is characterized by persistence of: IgA antibodies, CD4 helper T-cells and cytotoxic T-cells [323,324]. The following cytokines are expressed or elevated in the serum following VZV infections: Il-6, IL-10, IL-8, IL-17, IL-4, IL-12, IL-21, IL-23, and IL-1β as well as IFN-α and IFN-γ [266,322-331]. However, expression of IFN-α and IFN-β is upregulated in the early phases of VZV infection then IFN expression decreases significantly during the late phases of infection [324,327].

Specific complications of VZVinfections have specific cytokine profiles: (1) in patients with PHN, the serum levels of autoantibodies against: IFN-α, IFN-γ, GM-CSF, and IL-6 have been found to be markedly elevated [332]; (2) in patients with myelopathy and encephalopathy have elevated Cerebrospinal Fluid (CSF) levels of Matrix Metalloprotease (MMP)-3, MMP-8 and MMP-12, while patients with meningitis have significant increase in CSF levels of MMP-9 [333]; (3) in patients with VZV associated vasculopathy and giant cell arteritis there is: upregulation of IL-6, upregulation of IL-6 and VEGF-A, while programmed death-ligand 1 is downregulated [326]; and (4) in patients with ARN, the following cytokines are significantly elevated: IL-6, IL-8, IL-10, IL-18, IL-15, MIF, MCP-1, Eotoxin, IP-10, sICAM-1, and sVCAM-1, while low levels of the following cytokines have been encountered: IL-2, IL-4, IL-13, and IFN-α [334,335]. However, characterization of cytokine, chemokine and growth factor responses during different stages of VZV infection may facilitate the development of effective immunotherapeutic as well as vaccine strategies [336].

Signaling Pathways Involved in VZV Infections

The following signaling pathways are activated in VZV infections: Janus Kinase/Signal Transducer And Activation Of Transcription (JAK/STAT) pathway which is the most studied signaling pathway; c-Jun N-terminal Kinase (JNK) pathway; Extracellular Signal-Regulated Kinase (ERK/MEK) pathway; Phosphatidylinositol 3-kinase (PI3K/Akt) pathway; NK-κβ pathway; Mitogen-Activated Protein Kinase (MAPK) pathway; Wnt-Wingless pathway; and Cyclic-AMP Response Element Binding Protein (CREB) pathway [227,337-344].

The induction of the JAK/STAT pathway by IFNs leads to the upregulation of IFN-stimulated genes that are able to rapidly kill viruses within infected cells [345]. VZV downregulates STAT1 and JAK2 protein levels in virus-infected cells [346]. Activation of STAT3, a key regulator in inflammation and tissue regeneration, is critical for the life cycle of VZV because VZV skin infection is necessary for viral transmission and persistence in humans [347]. Survivin, which is abundant in cancers and tissues that contain proliferating cells, mediates a necessary virus-enhancing effect of STAT3 activation on VZV [347].

The ERK/MEK signaling pathway is influenced by VZV and the PI3K/Akt signaling pathway has an essential role in successful replication of VZV [338,340]. In addition, JNK pathway plays

an important role in lytic infection and reactivation of VZV in physiologically relevant cell types. MAPKs play a role in VZV infection of non-neural cells with distinct consequences in different cell types [339]. ORF-61 has an important role not only in the regulation of MAPK signaling pathway but also in VZV gene expression [344].

CREB, a factor involved in the regulation of several cellular processes, is activated upon infection of T-cells with VZV. CREB activation is important for VZV skin infection [341]. E3 ubiquitin ligase domain of ORF-61 is required to modulate NF-κβ signaling pathway, which is inhibited by VZV infection [228].

Conclusions and Future Directions

Apparently and as clearly shown in different sections of this review, VZV differs from other herpes viruses and it has the following peculiar features: having the smallest genome; losing almost all the genes that are not essential for its survival; being highly fusogenic and cell-associated; having no inhibitors of autophagy; being an exclusively human pathogen; having a species-specific and disease-specific cytokine profiles; and having an inverse relationship with glioma [1-5,7,13,74,159,348,349]. On the clinical side, the virus has shown BM stimulatory effects and several antitumor actions in patients with BM failure and HMs in addition to being associated with GVHD in recipients with HSCT [9,13,155-158,160,161,174,348,349].

The reported beneficial effects of VZV are rather outstanding and have translated into improved outcome and prolongation of OS in immunocompromised patients infected with VZV. These results should encourage researchers and scientists to give this potentially useful virus the attention it deserves. The positive effects of VZV on BM activity and on diseases such as BM failure syndromes, HMs, and solid tumors that occur through direct and indirect immunological mechanisms merit thorough investigations. The virus itself, modified or engineered versions of the virus or constituents obtained from the serum of patients infected with VZV may ultimately become extremely valuable therapeutic modalities in the management of patients with various BM failure, HMs, and solid tumors. Explanation of the stimulatory effect exerted on the three cell lines in the BM that is subsequently translated into increases in all blood counts as well as the antitumor effects of the virus may be provided by one or more of the mechanisms outlined or may be due to a new mechanism that needs to be elucidated.

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