The neurobiology of varicella zoster virus infection

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Abstract

Varicella zoster virus (VZV) is a neurotropic herpesvirus that infects nearly all humans. Primary infection usually causes chickenpox (varicella), after which virus becomes latent in cranial nerve ganglia, dorsal root ganglia and autonomic ganglia along the entire neuraxis. Although VZV cannot be isolated from human ganglia, nucleic acid hybridization and, later, polymerase chain reaction proved that VZV is latent in ganglia. Declining VZV-specific host immunity decades after primary infection allows virus to reactivate spontaneously, resulting in shingles (zoster) characterized by pain and rash restricted to 1-3 dermatomes. Multiple other serious neurological and ocular disorders also result from VZV reactivation. This review summarizes the current state of knowledge of the clinical and pathological complications of neurological and ocular disease produced by VZV reactivation, molecular aspects of VZV latency, VZV virology and VZV-specific immunity, the role of apoptosis in VZV-induced cell death, and the development of an animal model provided by simian varicella virus infection of monkeys.

Keywords

VZV; neurological disease; latency; apoptosis; animal model

Herpes zoster

As cell-mediated immunity to VZV declines with age or immunosuppression (as in organ transplant recipients and patients with cancer or AIDS), VZV reactivates from its latent state to cause zoster (shingles) characterized by dermatomal distribution pain and rash. Nearly 1,000,000 individuals in the U.S. are affected annually. Unlike varicella, which occurs primarily in the spring, there is no seasonal predilection for zoster. Zoster in young adults may be the first manifestation of HIV infection [1]. Varicella (chickenpox) in infancy predisposes to zoster earlier in life [2]. Like varicella, zoster skin lesions begin to resolve in less than a week, although pain normally lasts 4-6 weeks. Unfortunately, many patients experience chronic pain or postherpetic neuralgia (PHN). In chronic active VZV infection of ganglia, magnetic resonance imaging (MRI) has shown enhancement of ganglia and affected nerve roots [3]. Because VZV becomes latent in ganglia along the entire neuraxis, zoster can develop anywhere on the body. Zoster paresis (zoster with lower motor neuron type weakness) occurs in the arm, leg [4,5], diaphragm [6] or abdominal muscles [7].

The pathological features of zoster are characterized by inflammation and haemorrhagic necrosis with associated neuritis, localized leptomeningitis, unilateral segmental poliomyelitis, and degeneration of related motor and sensory roots [8,9]. Demyelination is seen in areas with mononuclear cell (MNC) infiltration and microglial proliferation. Intranuclear inclusions, viral antigen and herpesvirus particles have been found in acutely infected ganglia [10-13]. Antiviral drugs (e.g., valacyclovir, 1 g three times daily for 7-10 days) speed healing of rash and shorten the duration of acute pain. In immunocompromised patients, intravenous acyclovir (5-10 mg/kg three times daily for 5-7 days) is recommended.

Neurological complications of VZV reactivation

VZV reactivation causing shingles is often followed by chronic pain (PHN) as well as vasculopathy, meningitis/meningoencephalitis, myelopathy, cerebellitis and various ocular disorders, the most serious of which is retinal necrosis (Figure 1). VZV reactivation can also produce radicular pain without rash (zoster sine herpete). Importantly, all the neurological and ocular complications of VZV reactivation identified above may develop in the absence of rash. In addition, subclinical VZV reactivation (without pain or rash) has been demonstrated in astronauts [14], with shedding of infectious virus [15].

Postherpetic neuralgia (PHN)

PHN, operationally defined as pain that persists for at least 3 months and sometimes years after resolution of zoster rash, occurs in about 40% of patients over age 60 [16,17]. While the cause and pathogenesis of PHN are unknown, two non-mutually exclusive theories are that: (1) the excitability of ganglionic or even spinal cord neurons is altered after VZV-mediated damage; and (2) persistent or low-grade productive virus infection exists in ganglia.

Smith's [18] analysis of ganglia from an early case of PHN of 2.5 months' duration revealed diffuse and focal infiltration by chronic inflammatory cells (Figure 2A), an observation confirmed by Watson *et al*. [19] who found prominent collections of lymphocytes in ganglia from a patient with PHN of 2 years' duration (Figure 2B). The inflammatory response in ganglia of these subjects raised the possibility of prolonged viral infection. Further evidence that PHN may be produced by low-level ganglionitis comes from the detection of VZV DNA and proteins in blood MNCs of many patients with PHN [20-22], and from the favourable response of some PHN patients to antiviral treatment [23,24]. In a prospective, open-label phase I/II clinical trial, 15 patients with moderate to severe PHN were treated with intravenous acyclovir for 2 weeks, followed by oral valacyclovir for 1 month; 8 of 15 (53%) patients reported improvement of pain [25], warranting further investigation of antiviral therapy in a larger, randomized, double-blind, placebo-controlled trial.

VZV vasculopathy

VZV vasculopathy or stroke caused by productive virus infection of cerebral arteries is one of the most serious complications of VZV infection. VZV vasculopathy has also been referred to as granulomatous angiitis, VZV vasculitis/encephalitis, post-varicella arteriopathy, and herpes zoster ophthalmicus with delayed contralateral hemiparesis in a subset of patients with ocular and motor findings. Patients can present with fever, altered mental status, headaches and focal neurological deficits. In a study of 30 patients with VZV vasculopathy [26], 37% did not have rash preceding stroke and 33% had no cerebrospinal fluid (CSF) pleocytosis, making diagnosis difficult. In addition, 97% of patients had imaging abnormalities, often with characteristic lesions at grey-white matter junctions on MRI. Angiography in 23 of the 30 (70%) patients revealed focal arterial stenosis, occlusion, aneurysm or haemorrhage. Both large and small arteries were involved in 50%, small

arteries in 37%, and large arteries alone in only 13% of 30 patients. CSF of 30% of patients contained VZV DNA while 93% had anti-VZV IgG antibody in CSF, supporting previous studies that the detection of anti-VZV IgG antibody in CSF is a better test for diagnosing VZV vasculopathy than the detection of VZV DNA in CSF [27]. When CSF pleocytosis is present, cells are predominantly mononuclear and oligoclonal bands are present; the oligoclonal IgG is antibody directed against VZV [28].

The prevalence of VZV vasculopathy is unknown since stroke in the elderly is often attributed to atherosclerotic disease and the CSF is not examined in those patients. Even among immunocompromised patients with strokes, CSF is not routinely examined for anti-VZV IgG antibody. Two recent studies revealed an increased risk of stroke after zoster. An analysis of 7760 patients who had been treated for zoster and 23,380 controls found that the risk of stroke was 31% higher within one year after zoster and approximately 4-fold higher in patients with herpes zoster ophthalmicus (HZO) versus the comparison cohort [29]. Similarly, in a study of 658 HZO patients and 1974 controls, the risk of stroke was 4.52-fold higher in the patients than in controls [30]. To put this in perspective, the more than 500,000 annual cases of zoster expected even if all individuals over age 60 years in the U.S. received zoster vaccine would be at increased risk of stroke within the following year.

Studies of the pathogenesis of VZV vasculopathy have been limited since there is no animal model to study stroke caused by VZV. Case reports of VZV vasculopathy in which cerebral arteries were obtained at autopsy revealed virus in affected cerebral arteries, as evidenced by the presence of multinucleated giant cells, Cowdry A inclusion bodies, herpesvirus particles by electron microscopy, VZV DNA, and VZV antigen [31]. In chronic cases, virus is also found in areas of infarction, usually close to arteries and veins. Depending on the time elapsed since the onset of virus-mediated damage and on other possible unknown factors, a wide range of vascular involvement exists, from necrotizing arteritis to modest, chronic vascular inflammation, to thrombosis without inflammation, and remote vascular occlusion resembling atherosclerosis [32]. Recently, Salazar *et al*. [33] described an 80-year-old man who developed left ophthalmic distribution zoster and left-sided vision loss from ophthalmic artery occlusion. Before the diagnosis of VZV vasculopathy was established, giant cell arteritis was considered and a left temporal artery biopsy was performed. In contrast to a normal cerebral artery with no VZV antigen (Figure 3A), the asymptomatic left temporal artery contained VZV antigen in the adventitia (Figure 3B, red color). The presence of most VZV antigen in the adventitia of this early case of VZV vasculopathy supports the notion that VZV spreads transmurally from the adventitia to the intima, presumably after transaxonal spread to the artery via ganglionic afferent fibres [34,35]. Although it remains unknown why virtually all cases of VZV vasculopathy involve cerebral arteries rather than systemic arteries, it is possible that the absence of an external elastic lamina in cerebral arteries, unlike systemic arteries [36], facilitates transmural travel of the virus in cerebral arteries with continued virus production in a thickened intima.

VZV meningitis, meningoencephalitis, meningoradiculitis and cerebellitis

Acute VZV infection may also present as meningitis or a meningoencephalitis. Many reported cases of VZV encephalitis may actually be VZV vasculopathy [37]. Recent reports of VZV meningitis [38,39], meningoradiculitis [40] and cerebellitis (gait ataxia and tremor predominated) [41,42], all in the absence of rash and confirmed by the detection of VZV DNA and anti-VZV antibody in CSF, revealed that VZV is not an uncommon cause of aseptic meningitis.

VZV myelopathy

VZV myelopathy presents in various ways. One form is a self-limiting, monophasic spastic paraparesis, with or without sensory features and sphincter problems. This so-called post-infectious myelitis usually occurs in immunocompetent patients days to weeks after acute varicella or zoster. Its pathogenesis is unknown. The CSF usually contains a mild mononuclear pleocytosis, with a normal or slightly elevated protein. Steroids are used to treat these patients [43], although some improve spontaneously [44]. Rarely, VZV myelitis recurs, even in immunocompetent patients [45].

VZV myelopathy may also present as an insidious, progressive and sometimes fatal myelitis, mostly in immunocompromised individuals. Indeed, AIDS has commonly and increasingly become associated with VZV myelitis. MRI reveals longitudinal serpiginous enhancing lesions. Diagnosis is confirmed by the presence of VZV DNA or anti-VZV IgG or both in CSF [45]. Pathological and virological analyses of the spinal cord from fatal cases have shown frank invasion of VZV in the parenchyma [32] and in some instances, spread of virus to adjacent nerve roots [46]. Not surprisingly, some patients respond favourably to antiviral therapy [47-49]. Importantly, VZV myelitis may develop without rash. Early diagnosis and aggressive treatment with intravenous acyclovir has been helpful, even in immunocompromised patients [47]. The benefit of steroids in addition to antiviral agents is unknown. VZV can also produce spinal cord infarction identified by diffusion-weighted MRI and confirmed virologically [50]. Thus, VZV vasculopathy can cause stroke in the spinal cord as well as in the brain.

VZV retinal necrosis

VZV produces multiple ocular disorders, including both acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN). ARN develops in both immunocompetent and immunocompromised hosts. Patients present with periorbital pain and floaters with hazy vision and loss of peripheral vision. Treatment is typically intravenous acyclovir, steroids and aspirin followed by oral acyclovir [51]. Intravitreal injections of foscarnet and oral acyclovir have been used in early, milder cases. Although PORN can be caused by herpes simplex virus and cytomegalovirus, most cases are produced by VZV, primarily in AIDS patients with CD4+ counts typically less than 10 cells/mm^3 of blood [52], but also in other immunosuppressed individuals [53]. PORN may be preceded by retrobulbar optic neuritis and aseptic meningitis [54], central retinal artery occlusion or ophthalmic-distribution zoster [55], and may occur together with multifocal vasculopathy or myelitis. Patients present with sudden painless loss of vision, floaters and constricted visual fields with resultant retinal detachment. Multifocal, discrete opacified lesions begin in the outer retinal layers peripherally and/or posterior pole; only late in disease are inner retinal layers involved. Diffuse retinal haemorrhages and whitening with macular involvement bilaterally are characteristic findings. Treatment with intravenous acyclovir has given poor or inconsistent results [56], and even when acyclovir helped, VZV retinopathy recurred when drug was tapered or stopped. PORN patients treated with ganciclovir alone or in combination foscarnet had a better final visual acuity than those treated with acyclovir or foscarnet [57]. The best treatment for PORN in AIDS patients may be prevention with HAART, which appears to decrease its incidence [58].

Zoster sine herpete

Lewis [59] originally described multiple patients with dermatomal distribution radicular pain in areas distinct from pain with rash in zoster patients. Currently, most clinicians regard zoster sine herpete exclusively as the occurrence of chronic radicular pain without rash. The first two virologically confirmed cases of zoster sine herpete were verified by detection of

VZV DNA in CSF [60]. A third case of thoracic-distribution zoster sine herpete, in which electromyography of paraspinal muscles demonstrated frequent fibrillation potentials restricted to chronically painful thoracic root segments, was confirmed by detection of VZV DNA in blood MNCs and anti-VZV IgG antibody in CSF [61]. Recently, in a patient with zoster sine herpete, the CSF did not contain amplifiable VZV DNA, but did contain anti-VZV IgG with reduced serum/CSF ratios of anti-VZV IgG indicative of intrathecal synthesis [62]. Finally, the most compelling evidence that persistent radicular pain without rash can be caused by a chronic active VZV ganglionitis came from our analysis of a trigeminal ganglionic mass removed from an immunocompetent adult who had experienced relentless trigeminal distribution pain for more than a year. Pathological and virological analyses (Figure 4) revealed that the patient's zoster sine herpete was caused by an active VZV ganglionitis [63].

In recent years, the detection of VZV DNA and anti-VZV IgG antibody in patients with meningoencephalitis, vasculopathy, myelitis, cerebellar ataxia and polyneuritis cranialis, all without rash, has expanded the spectrum of neurological disease produced by VZV in the absence of rash. An illustrative example is provided by the report of an immunocompetent 45-year-old-woman who had multiple episodes of neurological disease (meningoencephalitis, multifocal vasculopathy, recurrent myelitis and inflammatory brain stem disease) over an 11-month period produced by VZV in which the CSF contained anti-VZV IgG antibody, but not VZV DNA, throughout her illness [64]. Overall, if the diagnosis of zoster sine herpete is suspected, the CSF and blood MNCs should be studied for VZV DNA, the CSF for the presence of anti-VZV IgG and IgM antibody, and the serum for anti-VZV IgM antibody.

VZV genome

The VZV genome was the first herpesvirus genome to be sequenced completely [65]. Currently, the complete DNA sequence of 24 independently obtained VZV isolates is available in the National Institutes of Health public access data base (http://www.ncbi.nlm.nih.gov/pubmed/). The VZV genome contains 71 open reading frames (ORFs) with the potential to encode 68 proteins (ORFs 42 and 45 are predicted exons from the same primary transcript, and ORFs 62, 63 and 64 are repeated as ORFs 71, 70 and 69, respectively). In addition to the predicted genes, three VZV genes have been experimentally detected: gene 33.5 [66], 9A [67], and ORF (S/L) [68]. Thus, VZV has the smallest alphaherpesvirus genome (125 Kb) with the coding capacity of 70 unique genes. The VZV genome is remarkably stable. Analysis of VZV propagated over 1206 passages in tissue culture cells reveals only three point mutations (E184G, N221D, and one silent) within the 834-bp ORF 63 [69]. Worldwide, VZV shows little geographic variation [70], although DNA sequencing has identified five VZV regional clades [71].

VZV pathogenesis

Upon initial exposure to aerosolized VZV, infected Langerhans cells along with mucosal and plasmacytoid dendritic cells carry the virus to resident T cells located within draining lymph nodes [72,73]. Infected T cells are induced to express skin homing factors and transport the virus to dermal fibroblasts and keratinocytes which in turn produce proinflammatory cytokines resulting in the vesicles characteristic of varicella [74-76]. Since afferent fibres of the sensory nervous system terminate in the skin, cell-free VZV present in varicella vesicles have direct access to dorsal root ganglia, cranial nerve ganglia and autonomic nervous system ganglia. Thus VZV, like herpes simplex virus (HSV)-1, the prototype neurotropic human alphaherpesvirus, can be transported along sensory nerve axons to the neuron, where latency is established [77,78]. Since varicella vesicles can

develop on any dermatome, all sensory ganglia can become latently infected, as evidenced by the detection of latent VZV DNA in cranial nerve, cervical, thoracic, lumbar and sacral root ganglia [79-81].

Along with axonal retrograde transport, neurons might be infected haematogenously, given the high virus load in blood during varicella (200-5000 copies of VZV DNA per 150,000 peripheral blood MNCs, 100-1000 VZV DNA copies per ml whole blood and 100-10,000 VZV DNA copies per ml serum [82,83]. Evidence for such a route of neuronal infection comes from the isolation of genotypically distinguishable strains of VZV from vesicles of a single individual during two separate episodes of virus reactivation despite only one episode of varicella [84]. Experimentally, the haematogenous route of neuronal infection is observed in monkeys infected with simian varicella virus (SVV), the primate counterpart of human VZV, with SVV DNA detected in ganglia even before the development of skin rash [85].

VZV-induced apoptosis in non-neuronal and neuronal cells

Apoptosis is a regulated form of cell death characterized by DNA fragmentation, membrane blebbing and cell shrinkage. This pathway proceeds through sequential proteolytic activation of caspases, a family of cysteine proteases. Two major pathways of apoptosis have been described. The extrinsic pathway is initiated by ligand interaction with death receptors resulting in activation of caspase-8. The intrinsic pathway is initiated when cytochrome c, released from damaged mitochondria, which activates caspase-9. Both caspases activate caspase-3, a biochemical marker for apoptosis, resulting in cell death.

VZV-induced apoptosis *in vitro* and *in vivo* has been reported in several cell types [86-88]. Analysis of the mechanism of varicella-induced apoptosis in SVV-infected monkey kidney (Vero) cells and in VZV-infected human melanoma (MeWo) cells showed that the induced apoptosis proceeds through the intrinsic pathway in both cases [89.90]. The intrinsic cell death pathway is determined by a balance between the proapoptotic (e.g., Bak and Bax) and anti-apoptotic (e.g., Bcl-2, Bcl-xL) mitochondrial Bcl-2 family of proteins. In addition, BH3-only proteins (e.g., Bad, Bim, Bid, Noxa and Puma) induce apoptosis by activating proapoptotic proteins or by neutralizing anti-apoptotic proteins. Real-time PCR and Western blot analyses revealed downregulation of Bcl-2 in varicella-infected cells, leading to release of cytochrome c from mitochondria and activation of caspase-9, a marker of the intrinsic apoptotic pathway.

Earlier, Hood *et al*. [91] reported that VZV induces apoptosis in human foreskin fibroblasts, but not in human sensory neurons. Recently, we developed an *in vitro* cell culture model to study the virus-neuron relationship. Neural stem cells (NSC) in the subgranular layer of the dentate gyrus of the hippocampus and subventricular zone of the lateral ventricle support neurogenesis in the adult brain. NSCs isolated from human fetal brain and cultured in suspension in the presence of epidermal growth factor produce spherical clusters known as 'neurospheres'. Depending on culture conditions, these self-renewing multipotent cells can be induced to differentiate into neurons, astrocytes and oligodendrocytes after adhesion to specific substrata. In fact, we obtained cultures containing more than 90% neurons, as confirmed by immunofluorescence staining for MAP2a, by inducing differentiation of NSCs in the presence of retinoic acid, dibutyryl cyclic AMP and neurotrophic growth factors (nerve growth factor and BDNF). Infection of these neurons with cell-free VZV did not lead to a cytopathic effect (CPE) even after 3 weeks, whereas a CPE developed within a week in human fetal lung fibroblasts infected with the same amount of VZV. VZV DNA and VZV-specific transcripts and protein were found in healthy-appearing neurons. Furthermore, the apoptotic markers TUNEL staining and caspase-3 activation were detected in VZV-infected

fibroblasts, but not in neurons. The relationship between inhibition of apoptosis and the establishment of VZV latency in neurons awaits further analysis.

VZV latency

In human ganglia, VZV establishes latency in the neuron [92-97]. The prevalence of latent VZV in the normal population has been variously reported as 63% [98], 79% [99], 87% [100], 91% [80], and 100% [101,102]. The largest study to date found latent VZV DNA in 94% of 414 trigeminal ganglia removed from 207 cadavers [103]. The VZV DNA burden during latency has also been variously reported as 6-31 [104], 258 ±38 [100], and 9,046 ±13,225 [101] copies per 100,000 ganglionic cells. The latter two studies are interesting since the same technique (real-time PCR) was used, and both studies detected similar amounts of latent HSV-1 DNA: 2902 ±1082 copies [100] and 3042 ± 3274 copies [101] per 100,000 ganglionic cells. The large range in VZV DNA burden during latency may reflect analysis of autopsy tissue collected many decades after primary infection and after multiple episodes of re-exposure to virus normally circulating in the population. Nonetheless, the VZV DNA copy number per latently infected neuron is too low to be detected with *in situ* technologies unless supplemented with prior *in situ* PCR amplification [94,105].

VZV gene expression is restricted during latency. Transcripts mapping to VZV ORFs 4, 18, 21, 29, 40, 62, 63 and 66 have been detected in latently infected human trigeminal ganglia [101,106-110]. The copy number of latently transcribed transcripts is extremely low. Among the VZV transcripts quantified by real-time PCR, ORF 63 transcripts are the most abundant and are present at ~3.7×10^3 copies per μg mRNA [109]. Considering that the average cell mRNA is 1.4 kb in length [111], the ratio of VZV ORF 63 to cell mRNA is, on average, $1:3.5 \times 10^8$. This low level of latent VZV gene transcription has hindered the global search of the VZV genome for active regions of transcription. The genome expression system (GeXP) is a new technical advancement which incorporates unbiased PCR amplification with fluorescence-labeled universal primers to simultaneously amplify multiple targets that are subsequently size-separated by gel electrophoresis on capillary tubes and detected after laser excitation [112,113]. The use of GeXP revealed multiple transcripts mapping to the entire VZV genome (the VZV transcriptome) in five independent PCR assays [114] and detected mRNA for VZV ORFs 4, 11, 29, 40, 41, 43, 57, 62, 63 and 68 in the VZV transcriptome of 26 latently infected human trigeminal ganglia [115]. Consistent with previous findings, VZV ORF 63 transcripts were the most frequent [101,109,115]; however, it should be noted that a distinct variability of VZV gene expression in latently infected ganglia exists (Figure 5) and not all VZV ORF transcripts are present in all ganglia. The detection of multiple transcripts corresponding to all stages of the virus life cycle clearly indicates that VZV latency differs from HSV-1 latency, where only a single latency-associated gene appears to be transcribed [116], although GeXP has not yet been used to study HSV-1 transcription in latently infected ganglia.

Identification of VZV proteins present during latency is hindered by the lack of suitable antibodies with sufficient specificity and sensitivity to detect low amounts of virus proteins in rare latently infected neuronal cells. Nonetheless, proteins encoded by VZV ORFs 4, 21, 29, 62, 63, and 66 have been detected in latently infected neurons [102,117-121]. Transcripts encoding these proteins have also been detected in latently infected ganglia [117,118,121]. However, only the one technique of immunohistochemistry has successfully detected latently expressed VZV proteins. Furthermore, a recent report suggested that the detection of VZV proteins during latency in human ganglia is a rare event confounded by the presence of lipofuscin, a potential source of non-specific staining [122]. Currently, all VZV proteins detected during latency are localized in the neuronal cytoplasm, including proteins localized to the nucleus during productive virus infection. This intriguing finding

may provide a clue to the maintenance of latency. Current efforts of numerous laboratories are exploring the mechanism of intracellular VZV protein localization and its outcome on productive virus infection.

VZV gene transcription is regulated at the epigenetic level during latency. The promoters for ORFs 62 and 63, VZV genes that are transcribed during latency, are associated with the histone protein H3 containing post-translational acetylation indicative of the euchromatic (transcriptionally active) state. Conversely, promoters for ORF 36 (thymidine kinase) and ORF 14 (glycoprotein C), VZV genes that are repressed during latency, lack enrichment in euchromatic modified histones [123]. That report remains the only confirmation in human ganglia of the concept of epigenetic regulation of neurotropic alphaherpesvirus gene transcription first described in animal models of HSV-1 latency [124]. Whereas latent HSV-1 gene regulation also involves microRNA silencing [125], no such microRNAs are present in human ganglia latently infected with VZV [126,127].

VZV-specific immunity

Primary VZV infection that induces varicella is followed by the production of VZV-specific antibody and VZV-specific T cell-mediated immunity [128,129]. Antibodies to VZV are detected throughout life, with the serum of individuals 60 to 94 years of age containing a variable presence of VZV-specific antibodies to VZV glycoproteins I-IV and to three non-glycosylated proteins; antibodies to VZV are also present in some elderly individuals with no history of varicella or zoster, indicative of subclinical infection [20]. Increased levels of antibody to VZV do not confer protection against zoster or PHN. In fact, increased levels of antibody to VZV after the onset of zoster are associated with more severe disease and a greater risk of PHN, perhaps because they reflect more extensive VZV replication [130].

T cell immunity to VZV is more important than the antibody response, as evidenced in studies of natural VZV infection in agammaglobulinaemic humans, who are unable to produce VZV-specific antibodies yet are protected against second episodes of varicella because of their ability to mount a VZV-specific T cell-mediated immune response [131]. Individuals with T cell-immune deficiency disorders have more severe disease than normal hosts [132], and a significant increase in the incidence of zoster is associated with immune suppression [133]. Even in human stem cell transplant recipients who received inactivated VZV vaccine, protection was correlated with VZV-specific T cell immunity, not with anti-VZV antibody [134].

VZV-specific T cell-mediated immunity maintains latent VZV in ganglia. The immune response can be subsequently boosted by subclinical reactivation of latent virus or environmental exposure to virus. Most importantly, the incidence of zoster increases with age as VZV-specific T cell-mediated immunity declines. For example, the frequency of VZV-specific memory CD4 T cells is significantly influenced by age as evidenced by their decrease during the first three years after varicella [135]. After mid-adult life, the intensity and quality of antigenic stimulation provided by re-exposure and asymptomatic reactivation are not sufficient to maintain VZV-specific T cell immunity. Furthermore, a comparison of the cell-mediated immune response to VZV antigen *in vitro* in young adults and individuals over age 60 revealed 5-fold fewer CD4 cells producing interferon-gamma or interleukin 4 and 5, as well as fewer CD4 early effectors and CD8 effector memory cells in the over age 60 group [136].

While reduced cell-mediated immunity with age or after exposure to immunosuppressive regimens in cancer patients or bone marrow transplant recipients results in VZV reactivation [137,138], virus-specific T cells are rarely seen in human ganglia latently infected with VZV [139]. Analysis of human ganglia from donors who had zoster 1-5 months before death

revealed VZV glycoprotein E (gE) in neurons and infiltration of non-cytolytic CD8+ T cells, but neurons that were positive for VZV gE were neither positive for MHC class I nor surrounded by T cells, suggesting that immune control of virus reactivation may not be dependent on direct contact with T cells [140]. Since VZV has been shown to down-regulate MHC I surface expression, virus latency is probably regulated by an innate immune response involving cytokines or chemokines [72,141,142]. CXCL10 has been proposed as a potential driver of T cell recruitment, based on its detection along with its receptor (CXCR3) in human ganglia from zoster patients [143].

Recognition of the essential role of cell-mediated immunity to VZV for protection against and recovery from varicella and zoster has led to studies designed to boost the cell-mediated immune response to VZV by immunization of elderly adults. Demonstration of the ability of zoster vaccine to reverse VZV-specific T cell deficiencies that were present before immunization was followed by the Shingles Prevention Study (see below).

VZV vaccine

There are two VZV vaccines, both of which contain live, attenuated virus. The first to be developed was the varicella (Oka strain) vaccine (Varivax, Merck) which has been used to vaccinate children to prevent varicella (chickenpox) in Japan since 1975 and in the US since 1996. The second vaccine (Zostavax, Merck) is used to prevent zoster in elderly individuals. The only difference between the two vaccines is that Zostavax contains 19,400 pfu per dose, 14-fold more virions than the varicella vaccine. Varivax generates VZV-specific humoral and cell-mediated immune responses, particularly CD8+ T lymphocytes [144]. The memory cell response that occurs after vaccination protects from infection during re-exposure to VZV.

Zostavax is a live, attenuated virus vaccine indicated for the prevention of herpes zoster in individuals 60 years and older. The most widely used measure of the cell-mediated immune response to VZV in elderly individuals before and after zoster vaccination has been the responder cell frequency [145]. Indeed, zoster vaccine administered to people over 60 years of age resulted in increased numbers of CD4 and CD8 cells, CD4 and CD8 effector memory T cells, and CD8 early-effector T cells; the half-life of the boost in T cell immunity to VZV is at least 5 years [146]. Zoster vaccine also boosts VZV-specific immunity in adults with a history of zoster before vaccination or with chronic illness.

The critical trial (Shingles Prevention Study, SPS) of the licensed zoster vaccine was a placebo-controlled, double-blind study of more than 38,000 adults over age 60 years and randomized to receive either zoster vaccine or placebo. All subjects were monitored for zoster. Endpoints included the burden of illness due to zoster and zoster-associated pain as well as the incidence of clinically significant PHN. Subjects received a single dose of Zostavax (n = 19,270) or placebo (n = 19,276). Racial distribution across both vaccination groups was similar: White (95%), Black (2%), Hispanic (1%) and other (1%). The gender distribution was 59% male and 41% female in both groups. The most common side effects reported by participants after zoster vaccination were redness, pain, itching, swelling, warmth or bruising at the injection site and sometimes headache. Varicella-like rashes at the injection site were more common in zoster vaccine than in placebo recipients (0.1% v. 6.4%; p < 0.05).

After a mean follow-up of 3 years, the SPS found that use of the Zostavax vaccine reduced the incidence of zoster by 51%. Subjects in the immunization group who developed zoster reported significantly less pain and discomfort than those in the placebo group, and PHN was less frequent (an overall 61% lower burden of disease). While the vaccine group had a significantly greater risk of a serious adverse event (1.9% v. 1.3%) and experienced more

adverse events at the injection site (48.3% v. 16.6%) than the placebo group during the first 42 days after vaccination, no significant differences were seen between zoster vaccine and placebo groups in the incidence of vaccine-related serious adverse events (both <0.1%) at the end of the study.

Baseline immunological measurements from the SPS confirmed that VZV-specific T cell immunity measured by responder cell frequency, as well as by ELISPOT assay, declined continuously with advancing age [147]. ELISPOT responses peaked at 2 weeks after immunization, with responses at 6 weeks post-immunization approximately 2-fold higher in immunized than in placebo recipients [148]. All values fell during the first year after immunization, but remained approximately 50% higher than pre-immunization levels for the 3-year study period. Importantly, the boost in VZV-specific T cell-mediated immunity was similar to that developing after naturally occurring zoster [130]. The magnitude of the boost in cell-medicated immunity to VZV was greatest in younger subjects, consistent with the efficacy of vaccine in preventing zoster which was greater in adults of age 60 to 69 years compared to those more than 70 years of age. The memory responses elicited in older subjects was similar to that seen after vaccination of the elderly with pneumococcal and influenza vaccines. Zoster vaccine was well-tolerated when administered concomitantly or sequentially with an inactivated influenza vaccine or pneumococcal vaccine.

Importantly, in immunized individuals who developed zoster, high VZV-specific cell-mediated immune responses were associated with reduced zoster severity and a lower frequency of PHN than in participants with lower VZV-specific cell-mediated responses, whereas a high humoral response was associated with increased severity of zoster and a higher frequency of PHN than in participants with a lower humoral immune response [130].

In the United States, the Center for Disease Control and Prevention Advisory Committee on Immunization Practices recommends zoster vaccine for all persons over the age of 60 years with no prior indications and in persons reporting a previous episode of zoster or who have chronic medical conditions. Although zoster vaccine is not recommended for immunocompromised individuals, it appears that the current zoster vaccine could be safely administered to several groups of moderately immunocompromised adult patients, such as VZV-seropositive HIV patients with CD4 T cell counts greater than 200 cells/ml, or even to patients with rheumatoid arthritis or psoriasis who are receiving moderate doses of methotrexate, steroids or tumour necrosis factor inhibitors [149]. In addition to the need to test the currently licensed zoster vaccine in moderately immunocompromised patients, higher titre zoster vaccines should be also tested for safety and immunogenicity, especially in light of reports of the safe administration of heat-inactivated VZV vaccine to autologous bone marrow transplant recipients and their accelerated recovery of cell-mediated immunity to VZV and reduced incidence of zoster [134,150].

By 2008, three years after zoster vaccine was licensed and recommended by the Advisory Committee on Immunization Practices for persons age 60 and older, less than 7% of the age group in the US was vaccinated [151]. This was due to a combination of lack of patient awareness regarding the availability of a vaccine, physicians' uncertainty about the duration of protection, and different cost-sharing plans for immunization. This is disappointing. Zoster vaccine should be universally administered to all individuals over age 60. Routine immunization is not currently recommended for people age 50-59 because of lack of efficacy data and cost-effectiveness information in this group, but consideration should be given to immunization of this population since 15% of zoster occurs between ages 50 and 59 years.

In the United Kingdom, the live attenuated vaccine against herpes zoster was approved for use in 2006. In England and Wales in people aged 60 or over, there were 88,650 cases and an estimated 18,200 people were still in pain after 3 months. In this age group an estimated 1750 people are hospitalized each year, and herpes zoster is given as the cause of death in 55 cases each year. Zoster generated an overall annual cost to the healthcare system of £17.3m (€20m; $24m), of which £11.5m was related to general practice and the remainder of secondary care. Almost 50% of the total costs related to disease in people aged over 80, because of the higher incidence and likelihood of complications in this group. Vaccination of 65-year-olds at 73.5% coverage was estimated to reduce the lifetime risk of zoster from 15% to 12%, or nearly 11,200 cases. It was also estimated that 1500 fewer cases of postherpetic neuralgia would occur each year, and that vaccination would reduce the annual number of hospitalizations by nearly 150. Vaccination of the 65-year olds was calculated to cost about £23.7m, but would result in savings to the health service of around £1.3m over the lifespan of the cohort, most of which would be saved in primary care. Results from this analysis suggest that immunization is likely to represent a cost-effective intervention for England and Wales, although there is a lost of uncertainty around the duration and range of vaccine-induced protection and the quality adjusted life year loss due to long-term pain. The most cost-effective age to vaccinate is 70 years, or 65 years if the vaccine does not offer additional protection against the severity of disease [152].

Several important questions regarding zoster vaccines remain. How many years will the current zoster vaccine maintain immunity to prevent zoster? Is zoster vaccine safe for immunocompromised individuals? Will a killed VZV vaccine produce a significant increase in cell-mediated immunity to VZV? Should multiple vaccinations of the elderly every decade of life after age 60 be considered? Should zoster vaccine be refined to include epitopes that induce cell-mediated immunity to VZV?

Attempts to produce varicella in animals

VZV produces disease only in humans. Experimental infection of small animals including mice [153], rats [154] and guinea pigs [155-159] by different routes resulted in seroconversion without productive infection (Table 1). Establishment of latent infection after corneal inoculation of mice could not be confirmed because VZV DNA was detected not only in ganglionic neurons, but also in non-neuronal cells in ganglia as well as in non-ganglionic tissue [160]. Nine months after foot-pad inoculation of rats, VZV nucleic acids as well as proteins were found in dissociated dorsal root ganglionic neurons in culture in the absence of clinical signs [161]. Because the ganglia were cultured 3-12 days before analysis, virus reactivation can not be ruled out. VZV gene 63 RNA and its encoded protein have been detected in sections containing ganglionic neurons from rats 18 months after inoculation [154,162]. However, virus DNA was found in both neurons and non-neuronal cells of rat ganglia 1-3 months after inoculation [163], unlike what is seen in humans. Thus the problem with the rat model is difficulty in distinguishing between a persistent and a latent infection or both. It is also possible that the pathogenesis of VZV infection in rats is different than in humans. Although viraemia and mild rash have been demonstrated in chimpanzees after subcutaneous inoculation of the vaccine strain of VZV (Oka) into the breast, ganglionic and non-ganglionic tissues were not studied [164]. In severely immunodeficient (SCID) mice implanted under the kidney capsule with human thymus or liver tissue followed by subcutaneous implantation of human skin or ganglia, virus infection and limited virus transcription in the ganglionic implants were detected after either skin or ganglia implantation [165,166]. Finally, reactivation of VZV has not been demonstrated in any of the above models.

Simian varicella virus (SVV) infection of primates as a model for human VZV infection

Virological and pathological features of SVV infection of non-human primates closely resemble those of VZV infection in humans [167-170]. Both SVV and VZV produce varicella, become latent and reactivate decades later to produce shingles (zoster) in their respective hosts. SVV and VZV belong to the alphaherpesvirus family and share 75% DNA homology. The genetic organization of the two virus genomes is similar [171]. Like VZV, SVV ORF 63 is translated in latently infected monkey ganglia [172].

VZV and SVV ORF 63 are present as duplicate copies of ORF 70 on their respective virus genomes. There are conflicting reports regarding the requirement of VZV ORF 63/70 expression for virus replication in culture [173,174]. Recently, we constructed a recombinant bacmid clone containing the complete SVV genome in which stop codons were inserted into both SVV ORFs 63 and 70. In contrast to the CPE that develops 3 days after transfection of Vero cells with wild-type SVV, a CPE did not develop until 10 days after transfection with the double mutant. Slow growth of the double mutant virus in culture indicated that while SVV ORF 63 is not required for replication in Vero cells in culture, its expression helps to produce robust virus replication (Mahalingham, unpublished observations).

Pathogenesis of SVV infection

Primary SVV infection in monkeys results in viraemia, as confirmed by the detection of virus DNA in peripheral blood MNCs [175-177]. Like disseminated VZV infection in humans, SVV infection is often disseminated, with liver and lung as the most affected organs [178]. Inflammation, haemorrhagic necrosis and eosinophilic intranuclear inclusions are seen in affected skin and viscera [175,177]. SVV also establishes latent infection in sensory ganglionic neurons at multiple levels of the neuraxis [179,180]. Natural infection of monkeys with SVV leads to establishment of latency in ganglia and reactivation after social and environmental stress [181] and after immunosuppression [182,183]. SVV is readily isolated from zoster rash [181].

Models of SVV infection in monkeys

Various models of experimental infection of monkeys with SVV have been established: (1) intratracheal inoculation of SVV into African green and Cynomologous monkeys [184,185]; (2) intrabronchial inoculation of rhesus macaques with SVV [172,186]; and (3) natural SVV infection by exposure of African green and Cynomologous monkeys to monkeys previously inoculated intratracheally [172,179,183].

In the first model, Cynomologous or African green monkeys inoculated intratracheally with SVV developed varicella rash at 7-10 days post-inoculation (dpi). SVV DNA was detected in blood MNCs at 3-11 dpi. Anti-SVV antibodies were detected 12 dpi, correlating with the resolution of varicella, and antibody titres remained stable for 4 months pi [170,176,187-191]. SVV was shown to infect ganglia before the appearance of varicella rash [85]. SVV DNA persisted in blood MNCs 7 days to 23 months pi, exclusively in T cells (CD4+, CD8+) at 23 months pi; however, virus could not recovered by cocultivation of blood MNCs with indicator cells [185]. SVV DNA and transcripts corresponding to putative immediate early (IE), early (E) and late (L) SVV genes were detected in liver, lung and ganglia at multiple intervals for 12 months [184].

Transcription of SVV ORFs 21, 29, 61 and 63 as well as antisense RNA with respect to ORF 61 was found in Vervet monkeys inoculated intratracheally multiple times with SVV [192].

In the second model, intrabronchial inoculation of rhesus macaques with SVV resulted in varicella rash followed by establishment of latency in ganglia along the entire neuraxis. Virological and immunological features of primary SVV infection and latency in these monkeys were similar, if not identical to, those of VZV infection in humans [172]. A proliferative burst of T cells was seen starting at 7 dpi and peaking at 14 dpi. Virus-specific CD4+ T cells also peaked at 14 dpi and reached stable levels at 73 dpi. Granzyme B-expressing CD4+ and CD8+ memory T cells, indicative of cytotoxic potential, appeared at 7 dpi and remained at high levels at least 28 dpi before decreasing to pre-infection levels. At 2 to 3 months after the resolution of varicella rash, SVV-specific DNA sequences were detected in ganglia, but not in liver or lung. RNA corresponding to SVV ORFs 21, 61, 62, 63 and 66 as well as antisense transcripts specific for SVV ORF 61, but not 40 (a late gene), was found in ganglia latently infected with SVV. Finally, like VZV, SVV ORF 63 protein was detected exclusively in the cytoplasm of neurons in latently infected ganglia (Figure 6).

The latency model above has been used to examine the potential reactivation of latent varicella due to delay in sampling ganglia after death. Two rhesus macaques, inoculated intrabronchially with SVV, were euthanized 12 weeks later and tissues were processed at different times following euthanasia. Analysis of SVV-specific DNA, RNA and ORF 63 protein in ganglionic and non-ganglionic tissues from the two monkeys showed that a 30-hour delay in time after death did not affect virus gene expression or the cytoplasmic localization of SVV ORF 63 [193].

In the third model, seronegative African green and Cynomologous monkeys were exposed to cage-mates previously inoculated intratracheally with SVV. Mild varicella developed at 10-12 dpi and virus DNA was detected by PCR in skin scrapings [179,183]. SVV DNA was only occasionally detected in blood MNCs. The establishment of latent infection was confirmed by detection of virus DNA in ganglia along the neuraxis and not in lung or liver. Furthermore, latent SVV DNA was localized exclusively in ganglionic neurons [180].

Experimental reactivation of latent SVV in monkeys

Using the third model described above, latent SVV infection was established in Cynomologous monkeys after which they were exposed once to X-irradiation and treated with tacrolimus and prednisone for 4 months. In one monkey, thoracic zoster was seen at 2 weeks after immunosuppression; the presence of virus antigen in biopsies of zoster rash was confirmed by immunohistochemistry, while the detection of transcripts specific for SVV capsid proteins in ganglia as well as the detection of virus glycoproteins in both ganglia and lung confirmed the presence of reactivated SVV [183].

Recently, SVV-latently infected African green and Cynomologous monkeys were treated with tacrolimus and prednisone as well as tacrolimus with or without exposure to X-irradiation (Table 2). None of 4 African green monkeys treated with tacrolimus and prednisone developed zoster, while 3 of 4 Cynomologous monkeys developed rash at 7-14 days after treatment with tacrolimus alone; zoster also developed in 1 of 4 African green monkeys at 42 days after X-irradiation and in all 4 African green monkeys at 10-14 days after X-irradiation and beginning of tacrolimus treatment. Thus, latent SVV was experimentally reactivated after immunosuppression with tacrolimus with or without X-irradiation as confirmed by immunohistochemical detection of virus glycoproteins in punch biopsies of zoster rash, in sections of lungs, and in multiple ganglia of most of the

immunosuppressed monkeys but not in control monkey tissues [186]. Virus glycoproteins were found to be better markers than nucleic acids to confirm virus reactivation in ganglia.

Subclinical SVV reactivation after irradiation of rhesus macaques latently infected with SVV resulted in disseminated varicella in another irradiated SVV-seronegative monkey in the same colony [194]. There are other reports of SVV reactivation in irradiated rhesus [195] and pig-tailed macaques [196,197]. Clearly, irradiation is an important contributing factor for SVV reactivation in non-human primates.

Monkey ganglia containing reactivated SVV await analyses of relevant components of the immune system to better understand virus pathogenesis and to develop strategies to counter disease produced by virus reactivation.

Acknowledgments

Abbreviations

ARN	acute retinal necrosis
CPE	cytopathic effect
CSF	cerebrospinal fluid
dpi	days post-inoculation
GeXP	genome expression system
HSV	herpes simplex virus
HZO	herpes zoster ophthalmicus
IgG	immunoglobulin G
IgM	immunoglobulin M
MNC	mononuclear cell
MRI	magnetic resonance imaging
NSC	neural stem cells
ORF	open reading frame
PHN	postherpetic neuralgia
PORN	progressive outer retinal necrosis
PCR	polymerase chain reaction
SVV	simian varicella virus
VZV	varicella zoster virus

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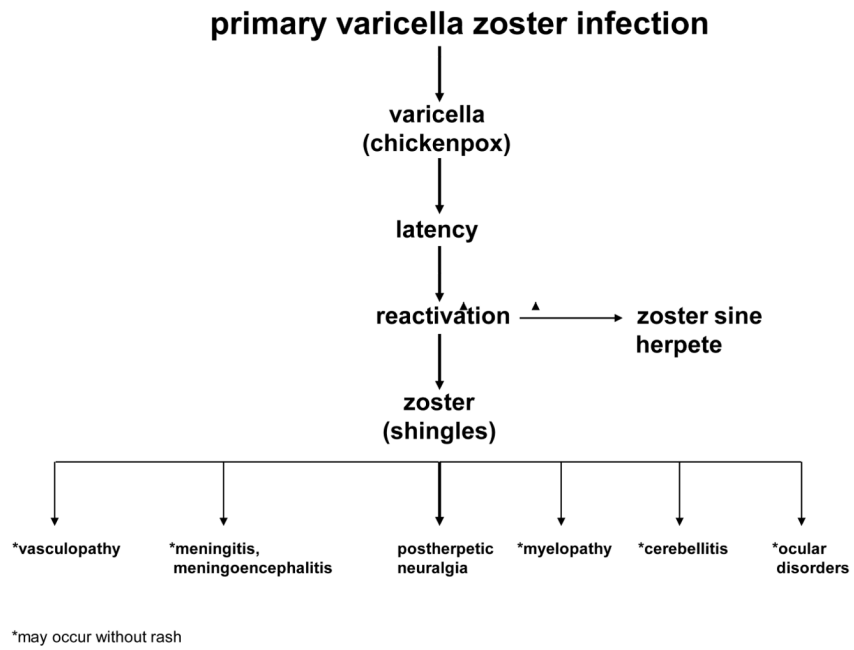
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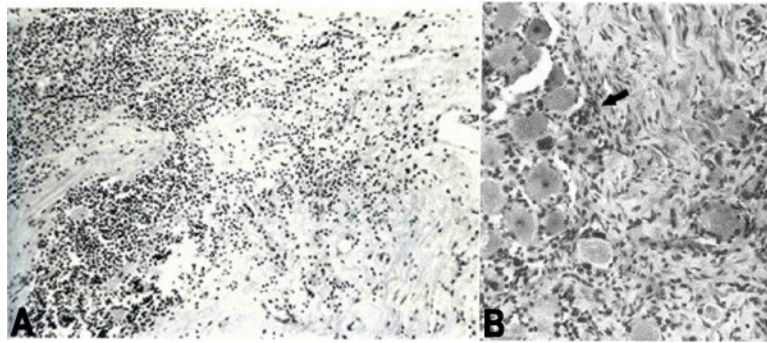
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primary varicella zoster infection

↓

varicella (chickenpox)

↓

latency

↓

reactivation ───→ **zoster sine herpete**

↓

zoster (shingles)

*vasculopathy   *meningitis, meningoencephalitis   postherpetic neuralgia   *myelopathy   *cerebellitis   *ocular disorders

*may occur without rash

Figure 1.
Neurological complications of varicella zoster virus reactivation.

Figure 2.
Haematoxylin and eosin-stained sections of dorsal root ganglia from patients with postherpetic neuralgia, revealing diffuse and focal infiltration by chronic inflammatory cells (A). Arrow in panel B points to a prominent collection of lymphocytes. Figure 2 previously published in Surg Neurol, 1978; 10:50-3; Smith FP; Pathological studies of spinal nerve ganglia in relation to intractable intercostal pain. Reprinted with permission of Elsevier, Copyright 1978.
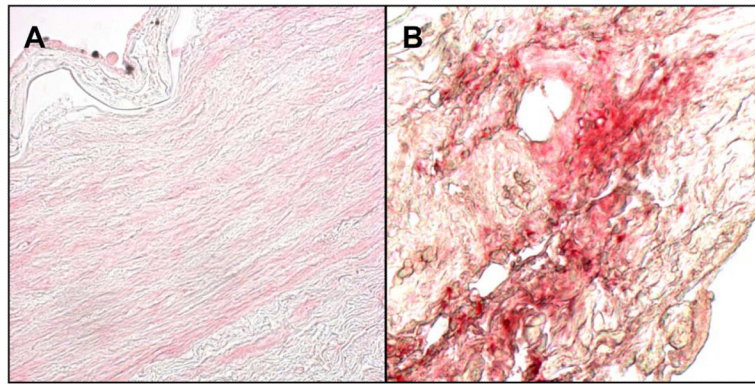
Figure 3.
Virological analysis of an asymptomatic left temporal artery from a patient with VZV vasculopathy. Sections of the temporal artery were deparaffinized and incubated with 10% normal sheep serum (NSS) in phosphate-buffered saline (PBS) for 1 hour at room temperature. To prevent non-specific binding, primary antibodies were adsorbed with normal human liver powder for 30 minutes and again for 20 hours at 4°C. Sections were then incubated with polyclonal antibodies raised against VZV ORF 63 protein (1:1000 dilution) or normal rabbit serum (1:1000 dilution), rinsed with PBS and incubated with a 1:300 dilution of biotinylated goat anti-rabbit IgG in PBS containing 5% NSS, washed 3 times in PBS, incubated with alkaline phosphatase-conjugated streptavidin (1:100 dilution) and washed three times with PBS. The color reaction was developed for 5-30 minutes with fresh fuchsin substrate system. Levimasole was added to the colour reaction to block endogenous phosphatase. Uninfected and VZV-infected BSC-1 cells were used as controls (not shown). The normal cerebral artery does not contain VZV antigen (A), whereas the temporal artery contains abundant VZV antigen in the arterial adventitia (B, red). Panels A, B 600X.
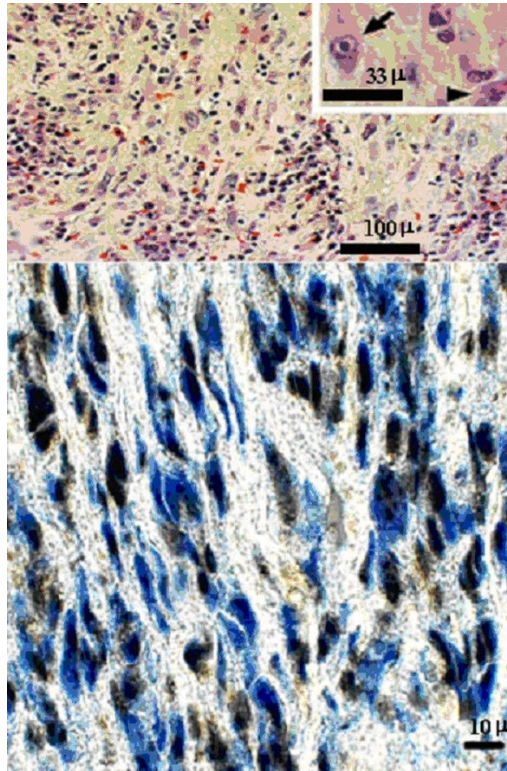
Figure 4.
Ganglionitis and intranuclear inclusions in zoster sine herpete. Haematoxylin and eosin staining of the trigeminal ganglion (top panel) shows widespread chronic inflammation with fibrosis and loss of neurons. Cells in some foci contain Cowdry type A intranuclear inclusions (arrow, inset) indicative of virus infection; the inflammatory cells are mainly lymphocytes with some plasma cells (arrowhead, inset). Immunohistochemical staining of the same ganglion (bottom panel) with mouse monoclonal antibody directed against VZV gene 63 protein indicates VZV antigen (brown staining) in multiple cells throughout the ganglion. Adjacent sections stained with antibody directed against HSV or with normal rabbit serum were negative (not shown).
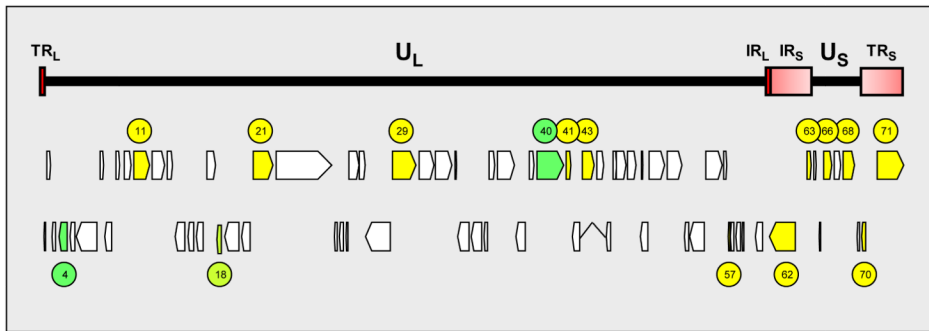
Figure 5.
VZV genes transcribed during latency. The VZV genome consists of ~125,000 base pairs of double-stranded DNA arranged in two units. The unique long segment (U_L) and unique short (U_S) segments are each bounded by internal and terminal invert repeat sequences (TR_L, terminal repeat of unique long, IR_L, internal repeat of unique long; IR_S, internal repeat of unique short; TR_S, terminal repeat of short [red shaded boxes]). The VZV genome contains 71 predicted open reading frames (ORFs) consecutively numbered from the leftward end of the virus genome. The entire VZV transcriptome has been identified in productively infected cells. In latently infected ganglia, VZV genes that have been sequence-verified include ORFs 11, 21, 29, 41, 43, 57, 62, 63, 66, 68, 70 and 71 (yellow). VZV ORF 4 and 40 transcripts have been detected by two independent techniques (PCR and *in situ* hybridization [dark green]), while VZV ORF 18 transcripts have been detected by only one technique (*in situ* hybridization [light green]).
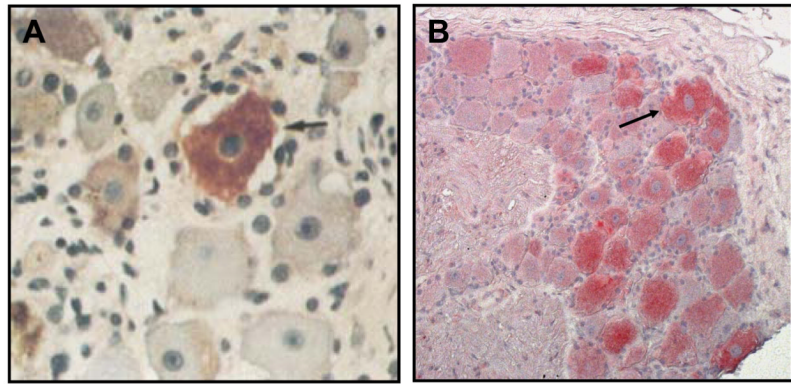
Figure 6.
Detection of VZV and SVV ORF 63 proteins in the cytoplasm of neurons in ganglia of a human latently infected with VZV and a rhesus macaque latently infected with SVV. Paraformaldehyde-fixed, paraffin-embedded sections of thoracic ganglia from a VZV-seropositive 46-year-old man (A) and from a rhesus macaque latently infected with SVV (B) were analyzed by immunohistochemistry using rabbit anti-VZV ORF 63. Both VZV and SVV ORF 63 proteins (arrows) are located exclusively in the cytoplasm of neurons in the respective ganglia.

Table 1

Results of attempts to produce VZV-induced disease in animals

Species	Route of inoculation	Sero-conversion	Rash (dpi)	Viremia	Time of sacrifice	Detection of SVV nucleic acids in tissue					Reference
						Ganglionic			Non-neuronal	Lung/liver	
						hyb[1]	PCR	Neuronal			
Chimpanzee	Subcutaneous	+	10	+	ND[2]	ND	ND	ND	ND	ND	[164]
Guinea pig	Intranasal/corneal	+	4	ND	ND	ND	ND	ND	ND	ND	[156]
Guinea pig	Intramuscular	+	9-25	+	23 d	+[3]	ND	ND	ND	+	[198]
Guinea pig	Intratracheal	+	–	ND	60 d	ND	ND	ND	ND	ND	[157]
Guinea pig	Ocular	ND	–	ND	21 d	ND	ND	ND	ND	ND	[199]
Guinea pig	Intramuscular	+	4-7	+	nd	NA[4]	NA	NA	NA	NA	[200]
Guinea pig	Subcutaneous	ND	+[5]	+	80 d	+[3]	+	ND	ND	ND	[159]
Guinea pig	Corneal	ND	NR[6]	ND	35 d	+[7]		+	–	ND	[158]
Rat	Subcutaneous	+	None	ND	9 m	+[7]	ND	+	ND	ND	[161]
Rat	Subcutaneous	ND	NR	ND	30 d	ND	ND	+	+	ND	[154]
Rat	Subcutaneous	ND	NR	ND	18 m	+[7]	+	+	+	ND	[162]
Rat	Subcutaneous	+	None	–	1-3 m	+[7]		+	+	ND	[163]
Rat	Intramuscular	ND	NR	ND	1 m		+	ND	ND	ND	[201]
Mouse	Subcutaneous	+	NR	ND	4-9 d	ND	ND	ND	ND	ND	[153]
Mouse	Corneal	+	None	ND	33 d	+[7]	+	+	+	ND	[160]
SCID-hu-mouse	Skin implants	NA	NA	ND	nd	ND	ND	ND	ND	ND	[165]
SCID-hu-mouse	Ganglia implants	NA	NA	NA	14 d	ND	+	+	–	ND	[166]

[1] hybridization

[2] not done

[3] dot blot

[4] not applicable

[5] dpi not reported

[6] not reported

[7] in situ.

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Table 2

Experimental reactivation of SVV in monkeys

Species	Treatment			Zoster rash		Reference
	Irradiation	Tacrolimus	Prednisone	Number positive/ number treated	Days post treatment	
Cynomologous	+	+	+	1/4	14	[183]
African green	−	+	+	0/4		Unpublished
Cynomologous	−	+	−	3/4	7-14	
African green	+	−	−	1/4	42	[186]
African green	+	+	−	4/4	10-14	