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Pathogenesis of Herpes Zoster: A Review

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Abstract

Herpes zoster, or shingles, is a localized disease characterized by unilateral radicular pain and a vesicular rash limited to the area of skin innervated by a single dorsal root or cranial sensory ganglion. Whereas varicella, or chickenpox, results from primary exogenous varicella-zoster virus (VZV) infection, herpes zoster is caused by reactivation of endogenous VZV that has persisted in latent form within sensory ganglia following an earlier episode of chickenpox. In contrast to recurrent herpes simplex, herpes zoster is commonly associated with severe pain: prodromal pain often precedes the rash by several days; pain usually accompanies the dermatomal rash of herpes zoster; and clinically significant pain and allodynia may persist for weeks, months, or even years after the herpes zoster rash has healed, a debilitating complication known as *postherpetic neuralgia* (PHN). The incidence and severity of herpes zoster and PHN increase with age in association with an age-related decline in cell-mediated immunity to VZV. The Shingles Prevention Study—a randomized double-blinded placebo-controlled trial—sought to evaluate the capacity of a live attenuated VZV vaccine to protect older adults from herpes zoster and PHN by boosting their waning cell-mediated immunity to VZV. The study demonstrated that the zoster vaccine produced significant reductions in the incidence of herpes zoster, in the burden of illness caused by herpes zoster, and in the incidence of PHN.

Keywords: Pathogenesis, Herpes Zoster, *postherpetic neuralgia* (PHN)

1. Introduction

Pathogenesis

Nasopharyngeal replication of varicella zoster virus occurs immediately after primary infection. It is followed by spread of infection to adjacent lymphoid tissue where the virus infects memory CD4⁺ T cells which are abundant in tonsillar lymphoid tissue. Trafficking of memory cells expressing cutaneous homing antigen and chemokine receptor 4 (CCR4) to the skin is thought to deliver virus to cutaneous epithelia within a few days of infection^[1]. The localized replication in epithelial cells is facilitated by down-regulation of interferon- α within the infected cells and failure of induction of adhesion molecules^[2].

At the same time cell-to-cell spread of virus appears to be contained for the first week by production of interferon- α in adjacent epithelial cells. Thereafter, the virus overcomes the innate defenses and vesicles appear. Production of cytokines and up-regulation of capillary endothelial adhesion factors attract migratory T cells that may further spread virus before they contain viral replication^[2] (figure 1)

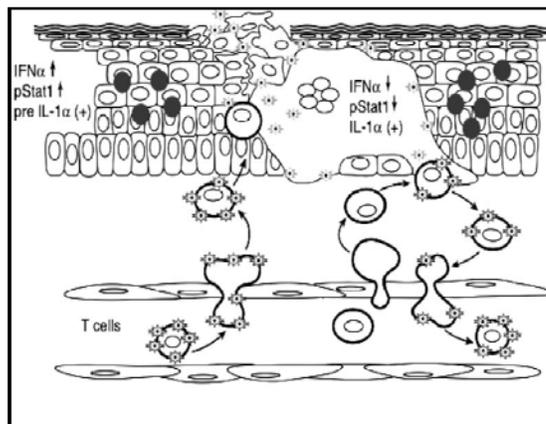


Fig 1: illustrates new concepts about VZV pathogenesis.

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A diagram depicting proposed events in the pathogenesis of VZV infection of skin. According to this model, T cells within the tonsillar lymphoid tissues become infected by VZV transfer into these migratory cells of the immune system following the initial inoculation of respiratory epithelial cells with the virus. Infected T cells enter the circulation and transport the virus to the skin shortly thereafter, exiting through capillary endothelium by the usual mechanisms for trafficking of migratory T cells. The infected T cells then release infectious VZV at skin sites of replication. The remainder of the 10- to 21-day incubation period is the interval required for VZV to overcome the innate IFN response in enough epidermal cells to create the typical vesicular lesions containing VZV at the skin surface. Signaling of enhanced IFN production in adjacent skin cells prevents a rapid, uncontrolled cell-cell spread of VZV. Additional “crops” of varicella lesions may result when T cells traffic through early-stage cutaneous lesions, become infected, and produce a secondary viremia. This process continues until host immune responses trigger the up-regulation of adhesion molecules and mediate the clearance of the virus by VZV-specific antiviral T cells.

Cell-free virus which is present only in skin vesicles is necessary for the infection of sensory nerve endings in epithelia. This result in virus migration up sensory axons to establish latency in sensory ganglia [3]. The final assembly and envelopment of newly synthesized virions occurs within specialized wrapping cisterna located in the trans-Golgi network [4, 5]. The concave face of each wrapping cisterna is rich in varicella zoster virus glycoproteins and becomes the viral envelope. The convex side is rich in cellular proteins such as cation-independent mannose 6-phosphate receptors and the cisterna becomes a transport vesicle containing the newly enveloped virion [4, 6]. In human embryo lung fibroblasts, the presence of cation-independent mannose 6-phosphate receptors on the convex face of the wrapping cisterna is postulated to route virions from the cell secretory pathway to endosomes where the virions are sequestered [7, 8] (figure 2)

Varicella zoster virus also spreads quickly to adjacent epidermal cells by inducing the fusion (mediated by glycoproteins H, L, B and E) of virally infected cells with uninfected neighbouring cells. In contrast, the loss of cation-independent mannose 6-phosphate receptors in keratinocytes in the superficial epidermis allows for the accumulation of cell-free virions, which are necessary for transmission and establishment of latency [9].

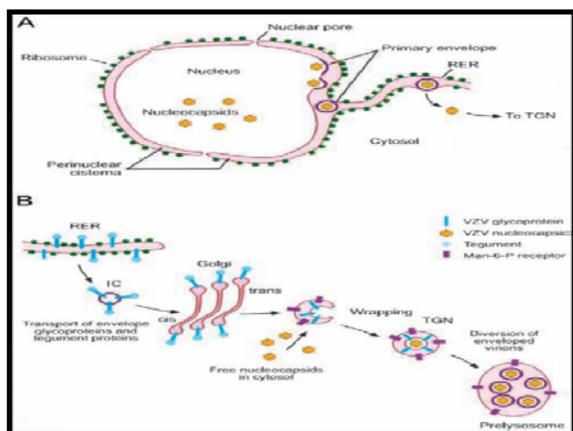


Fig 2: showing the Intracellular transport and maturation of varicella-zoster virus (VZV).

A, Primary envelopment. VZV nucleocapsids assemble in the nucleus, bud through the inner nuclear membrane and acquire a temporary envelope before entering the perinuclear cisterna, which is continuous with the lumen of the endoplasmic reticulum. The primary virion envelope fuses with the membrane of the endoplasmic reticulum, delivering naked nucleocapsids into the cytosol. **B, Glycoprotein transport and virion assembly.** VZV glycoproteins are synthesized in the rough endoplasmic reticulum (RER) and become processed and transported to the Golgi complex via the intermediate compartment (IC) independently of newly assembled nucleocapsids. From the RER, the glycoproteins, together with adhered tegument proteins, are transported to the trans-Golgi network (TGN), where they concentrate in the concave membrane of specialized wrapping TGN cisternae. The viral nucleocapsids converge with the glycoproteins and tegument as the TGN sacs wrap around the nucleocapsids and fuse, giving rise to mature virions. The VZV glycoprotein-rich membrane of the concave face of the wrapping cisterna becomes the viral envelope. The membrane of the convex face is rich in mannose 6-phosphate (Man-6-P) receptors and delimits a transport vesicle that encloses the newly enveloped virion. Man-6-P receptors on the membrane of the convex face of the wrapping cisterna are thought to route viral particles from the cell secretory pathway to endosomes where the virions are degraded.

A guinea pig model of latency and reactivation *in vitro* has been developed. Neurons dissected from the myenteric plexus were propagated in culture. In this model, infection of sensory nerve endings with cell-associated virus causes lytic infection, whereas cell-free virus establishes latency [37]. Latently infected human ganglia show restricted expression of 6 genes (i.e. open reading frame) *ORF4*, *ORF21*, *ORF29*, *ORF62*, *ORF63* and *ORF6* [10, 11]. The same pattern of expression is found in latently infected guinea pig somatic neurons. The addition of cell-associated virus, results in varicella zoster virus reactivation and lytic infection. Open reading frame 61 protein is absent from cell-free virions which are able to establish latency in the gut ganglia. More recently, direct transfer of varicella zoster virus has been demonstrated from infected peripheral blood mononuclear cells to ganglion tissue implanted into SCID-hu mice. Direct transfer of virus to the ganglion and establishment of latency by this route may therefore be possible [12].

In addition to detection of messenger RNA from the 6 ORFs mentioned, immunohistochemical studies have shown the presence of protein products from ORFs 4, 21, 29, 62, 63 and 66. Moreover, these are located in the cytoplasm of infected cells, whereas in lytic infection both cytoplasmic and nuclear localization is evident. A working hypothesis is that phosphorylation of immediate-early protein 62 by the protein kinase encoded by *ORF66* prevents translocation of the former to the nucleus which in turn interrupts the cascade of viral transcription and replication [13]. The addition of ORF 61 protein to the latently infected guinea pig neuron model results in translocation of immediate-early protein 62 and the ORF 29 protein to the nucleus. This causes transcription of a, b and g viral proteins and reestablishment of lytic infection.

The incidence of herpes zoster increases with age and with other causes of decreased cellular immunity. Limiting dilution experiments have established that reduced varicella zoster virus T cell responder cell frequency characterizes all conditions associated with increased varicella zoster virus reactivation [14]. Much of the T cell response in latently

infected individuals is directed against glycoprotein's E, H, B and I as well as against transcriptional activators encoded by ORFs 4, 10, 62 and 63. Boosting of the cell-mediated immune response has been shown in mothers of children with varicella, suggesting that exposure to antigen may be important for maintaining immunity^[15]. Two studies have shown that the incidence of herpes zoster is lower in adults with greater contact with children in their daily lives which was considered to be a surrogate for exposure to varicella zoster virus^[16, 17]. Proof that exposure to exogenous antigen is protective came with the recent demonstration that a live attenuated varicella zoster virus vaccine reduced the incidence of herpes zoster and the burden of disease compared with placebo^[18]. Reducing the occurrence of herpes zoster will be crucial to eliminating transmission of varicella zoster virus. The force of infection (i.e. the rate at which individuals acquire infection after exposure) is estimated to be 20% for varicella leading to infection of children 2–4 years of age. By contrast, the estimated force of infection for herpes zoster causing varicella is 0.1%^[19]. Thus, susceptible children are more likely to develop varicella from exposure to varicella than from exposure to herpes zoster. Nonetheless, herpes zoster will become a more common source of varicella as immunization programs eliminate varicella, this is already evident in cases of nosocomial varicella in the United Kingdom, where many cases arise from contact with HZ rather than varicella^[20].

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