VARICELLA ZOSTER VIRUS-ITS PATHOGENESIS, LATENCY & CELL-MEDIATED IMMUNITY

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Abstract

Varicella zoster virus causes primary infection as chickenpox, at which time latency is established in the neurons of the dorsal root ganglia or ganglia of the cranial nerves. Reactivation produces herpes zoster infection (HZI), commonly called shingles. An understanding of the mechanisms of latency is crucial in developing effective therapies for VZV infections of the nervous system. This article describes the pathogenesis of VZV which includes immune response to the virus, immune evasion by the virus, mechanism of its latency and cell-mediated immunity.

Key words: Herpes virus, latency, ganglia, Varicella zoster virus, VZV.

Introduction

Varicella Zoster Virus (VZV) is one of eight herpes viruses known to infect humans. It is a virulent virus of the herpes family. Infection by VZV has a worldwide distribution.[1] VZV is closely related to the herpes simplex viruses (HSV), sharing much genome homology. The known envelope glycoproteins (gB, gC, gE, gH, gI, gK, gL) correspond with those in HSV. VZV also fails to produce the latency-associated transcripts. VZV virions are spherical and 150-200 nm in diameter. Their lipid envelope encloses the nucleocapsid of 162 capsomeres arranged in an icosahedral form. Its DNA is a single, linear, double-stranded molecule. The capsid is surrounded by a number of loosely associated proteins known collectively as the tegument; many of these proteins play critical roles in initiating the process of virus reproduction in the infected cell. The tegument is in turn covered by a lipid envelope studded with glycoproteins that are displayed on the exterior of the virion. VZV has developed a complex strategy that allows it to remain latent in the body and avoid destruction by the immune system.

Pathogenesis

Primary infection with VZV leads to varicella (chicken pox). The virus then travels from the skin to sensory nerves. Once in the sensory nerves, the virus moves to the sensory ganglia where it becomes latent. If reactivated, the virus travels from the sensory ganglia back to the skin where it produces herpes zoster infection (HZI), commonly called shingles(Figure 1).[2] The mode of transmission is by airborne droplets or direct contact with infected lesions, with the probable portal of entry being the respiratory tract. Mostly, primary and recurrent VZV infections are symptomatic, and asymptomatic virus shedding does not appear to occur with VZV.[3,4,5] Histopathological appearance of the skin lesions of herpes zoster and chickenpox are identical: both contain multinucleated giant cells with

eosinophilic intranuclear inclusion bodies. The rash of herpes zoster is restricted to one area of the skin on one side of the body along the dermatome innervated by the ganglion in which the latent virus has reactivated. Also, the lesions of herpes zoster consist of closely grouped vesicles on an erythematous base, whereas those of chickenpox are individual and randomly distributed. These differences reflect intraneural spread of virus to the skin in herpes zoster, in contrast to viremic spread in chickenpox.[6]

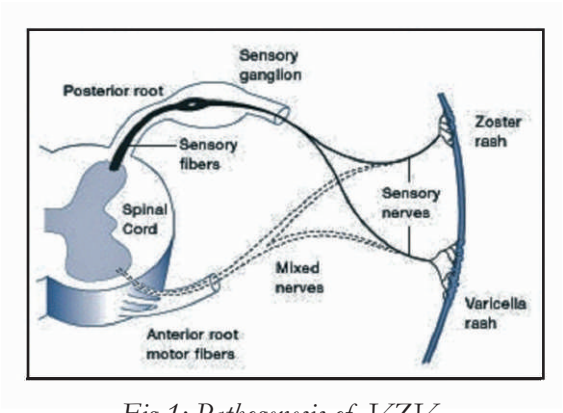

Fig 1: Pathogenesis of VZV.

Immune response to the virus

VZV presents many proteins to the immune system. Antibodies to the viral glycoproteins can neutralize the ability of virus to infect cells. Cellular immunity is more important than humoral immunity, both for limiting the extent of primary infection with VZV and for preventing reactivation of virus with herpes zoster. Children with congenital T-cell defects or AIDS are more likely to develop disseminated chickenpox and zoster than those with B-cell abnormalities. Infection with VZV induces production of cytotoxic T cells that recognize and destroy virus-infected cells. Cytotoxic T cells can recognize cells expressing glycoproteins gB, gC, gE, gH, and gI as well as the IE62 and IE63 tegument proteins. Cytotoxic T cells specific to VZV that are obtained from immune persons are class I or class II MHC restricted.[7]

Immune evasion by the virus

Although the immune system has many ways to destroy virus-infected cells, VZV has evolved several mechanisms to reduce presentation of viral proteins to the immune system and thereby evade detection.[8] The virus remains latent in the sensory ganglia for the lifetime of the host and limits its expression of viral proteins during latency. VZV may evade the immune system by downregulating expression of MHC class I antigens on the surface of infected cells. In addition to limiting MHC class I trafficking to the cell surface, VZV-infected cells are resistant to the upregulation of MHC class II expression elicited by interferon-γ.[9] When cells are infected with viruses, viral proteins are broken down inside the cell. On the surface of the infected cells, MHC class I molecules present portions of these proteins to cytotoxic T cells that can kill the virus-infected cells. Infection of human fibroblasts with VZV causes reduced levels of MHC class I molecules on the surface of infected cells compared with uninfected cells. By reducing surface expression of these proteins and limiting presentation of viral peptides to cytotoxic T cells, virus-infected cells may escape destruction by the immune system.[10]

Latency And Varicella Zoster

Latency is a state in viral infection in which the viral genome is present in non-replicating stage in an infected cell, but can become active intermittently.[11] An understanding of the mechanisms of latency is crucial in developing effective therapies for VZV infections of the nervous system.[12] Establishment of latency is contributed by host factors like neurons, IgG, CD8 +cytotoxic T-lymphocytes & cytokines and viral factors include down regulation of α-gene expression and DNA replication.[11] It is now established beyond doubt that latent VZV is predominantly located in human ganglionic neurons. Latent stage is maintained by viral genes expressed primarily during latency. Virus gene transcription during latency is epigenetically regulated, and appears to be restricted to expression of at least six genes, with expression of gene 63 being the hallmark of latency.[13] Expression of these

latency-associated genes may function to keep the viral genome from being digested by cellular ribozymes or being found out by the immune system.[11]

During chickenpox, infectious virus that is present in large amounts in chickenpox vesicles enters the endings of sensory nerves in the skin, travels up the sensory nerves to the dorsal root and cranial sensory ganglia where the nerve cell bodies are clustered, and establishes lifelong residence (ie, latent infection) in those sensory neurons. Consequently, the dorsal root and cranial sensory ganglia of everyone who has had chickenpox are latently infected with VZV—they contain the genomic DNA of VZV, but not infectious virus.

In infected cells, VZV DNA replication results in a diverse population of molecules ranging from unit-length genome, double-stranded, linear or circular genomes to large replicative intermediates consisting of multiple genomes looped and tangled together. These structures resolve during latency and the virus genome is present in circular, episomal form in the nucleus of neuron which is silent to immune system.[14] VZV genes 21, 29, 62, 63 and 66 have been detected in latently infected human ganglia.[15,16] But quantitative analyses demonstrated that VZV ORF 63 is the most abundant and prevalent of the latently transcribed genes.[17] Since the protein encoded by VZV 63 is present in latently infected neurons, VZV 63p is the most likely candidate VZV gene expressed during latency to contain an anti-apoptotic function, thus inhibit apoptotic action of infected human ganglia in vitro.[18]

Analysis of human trigeminal ganglia shows lack of T cells around the neuron containing latent VZV.[19,20] Viral proteins encoded with the genes 21, 29, 62, 63 and 66 are present in the cytoplasm of latently infected human trigeminal ganglion. Viral protein encoded with VZV gene 66 found to down regulate the expression of MHC class I expression.[21] It is possible that major histocompatibility complex (MHC) presentation is blocked. Virus-specific mechanism to inhibit MHC presentation coupled with the naturally low expression of MHC on neurons results in lack of CD8-T cell migration around human ganglion infected with VZV.[21]

This latent VZV eventually reactivates, presumably in a single sensory neuron, to cause herpes zoster. The reactivated virus multiplies and spreads within the ganglion, infecting many additional neurons and supporting cells—a process that causes intense inflammation and neuronal necrosis. The virus then travels from the sensory ganglion back down the nerve to the skin, where it produces the characteristic dermatomal rash of herpes zoster.[6,22,23]

VZV is presumed to persist in latently infected cells as an episome, rather than by integration into cellular DNA;[24] persistence must occur without translation of the full sequence of viral gene products, because virion production would be expected to be associated with cell lysis. Although the assessment of viral load in ganglia is difficult, quantitative DNA PCR analysis of human trigeminal ganglia suggests the presence of about 250 VZV genome equivalents per 105 cells.[25] The estimates of virus burden suggest that VZV persists in more cells of the trigeminal than thoracic ganglia, which could explain the relatively higher incidence of facial zoster. When reactivation occurs, extensive viral replication takes place within the cells of the sensory ganglia, producing pathologic changes including extensive infiammation and necrosis.[26] The virus moves to the skin innervated by the involved ganglion via axonal transport, causing the dermatomal rash of typical herpes zoster.

The mechanism that account for maintainance of latency and subsequent reactivation remain unknown. Predisposing factors for the reactivation of VZV includes: immunosuppressed conditions, cytotoxic drugs, radiation, old age, alcohol abuse, malignancy or tumor of dorsal root ganglia, dental manipulation.

Cell-mediated Immunity

In addition to establishing latent VZV infections in sensory neurons, chickenpox elicits an immune response that limits the ability of the latent virus to reactivate and cause herpes zoster.[27] The level of this immunity to VZV gradually declines over time but is periodically boosted by subclinical infections resulting from exogenous exposure to VZV and by episodes of reactivation limited by rapidly mobilized immune responses so that no rash develops. These abortive cases of herpes zoster is called "contained reversions" and noted that they could sometimes result in pain in the corresponding dermatome without the development of a rash, a syndrome called zoster sine herpete.[4,5,23] It was found that the antibodies to VZV can provide protection only against primary exogenous VZV infection (ie, chickenpox). It has no role in host resistance to herpes zoster. Instead, it is the VZV-CMI that limits the ability of latent VZV to reactivate and cause herpes zoster.[28]

Conclusion

Varicella zoster virus, one of the three human alpha herpes viruses, causes serious neurologic disease upon reactivation. VZV latency research is limited due to the lack of a small animal model in which virus latency can be established and experimentally reactivated. In addition, we do not know the extent of disease produced by VZV reactivation. Future efforts are required to expand the scope of our knowledge concerning disease produced by VZV reactivation and the mechanism of virus latency.

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