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Varicella zoster virus immunity: A primer

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Summary Varicella zoster (VZV) is among the most prevalent viruses affecting the human race. The majority of us experience primary infection as varicella in childhood and remain latently infected, with occasional reactivation as the infectious entity, shingles. Rarely, VZV causes severe and disseminated disease, which can be fatal despite the availability of highly active antiviral agents. VZV is the only herpesvirus against which effective vaccines have been developed and widely implemented in several countries, further complicating its epidemiology. The immunological correlates of protection against varicella remain incompletely understood. Here we provide a brief overview of evidence from animal models and observational studies that define immunologic risk factors for severe varicella, and thus the most important elements of VZV immunity. Although circulating VZV-specific antibody can prevent primary infection, innate and cellular responses appear much more important in limiting its severity and duration. Improved understanding of these protective factors may assist us in developing more effective strategies for the prevention and treatment of severe varicella.

Introduction

Varicella zoster virus (VZV) is a human-restricted alphaherpesvirus of the genus *Varicellovirus*. The VZV genome is a linear double-stranded DNA molecule of 125,000 base pairs (including a unique long region of 105,000 bp and a unique short region of 5232 bp, as well as internal repeat and terminal repeat regions).[1] Genomes are packaged into an icosahedral nucleocapsid surrounded by a tegument layer consisting of regulatory proteins and encapsulated by a host-derived lipid envelope containing viral glycoproteins.[1]

VZV encodes 71 unique open reading frames (ORFs), of which around one third are dispensable for viral replication *in vitro*; genes essential for viral replication are conserved across the herpesviruses.[2] Despite the existence of at least 5 distinct clades of VZV, these share 99.8% sequence homology, indicating a high degree of genetic stability.[1] The

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consensus model for VZV replication is based on studies of herpes simplex virus (HSV).[2] Briefly, attachment via envelope glycoproteins leads to entry, translocation of the uncoated nucleocapsid, docking at nuclear pores and injection of vDNA into the host nucleus. vDNA replication and nucleocapsid assembly occurs in the nucleus, followed by budding across the nuclear membrane. Virion assembly occurs in the trans-Golgi network, where nascent virions undergo secondary envelopment prior to vesicular trafficking to the plasma membrane. Most virions remain cell-bound via viral glycoprotein-receptor interactions.[2]

There are three phases to VZV infection (primary infection, latency and reactivation), resulting in two distinct disorders: varicella (chickenpox) due to primary infection; and herpes zoster (shingles) due to reactivation from asymptomatic latency: the immune system must limit both the severity of VZV disease and the frequency of VZV reactivation(s).

Primary VZV infection results from droplet transmission at the airway epithelium, having an incubation period of 10—21 days. VZV is tropic for T cells, dendritic cells, epithelial cells and neurons.[2] It is thought that mobile infected leucocytes recirculating from the upper airway epithelium seed infection within the lymphoid tissues.[2,3] Subsequent systemic dissemination, again via infected T cells, is thought to result in widespread skin foci of viral replication.[2,4,5] VZV infection of the epidermis promotes the formation of blisters containing high-titer infectious virus that presumably facilitates onward transmission.[6] In temperate climates, varicella is an endemic disease of early childhood, with markedly seasonal variation in incidence.[7] Over 80% of children in Europe are seropositive by age 10.[8] Complications of varicella include secondary bacterial skin and soft tissue infections or, less commonly, central nervous system involvement. Severe overwhelming varicella (pneumonitis, encephalitis, hepatitis and multi-organ failure) occurs rarely in children: In England and Wales the incidence of hospitalization in children is approximately 16 per 100,000 person years and the case fatality is less than 1 per 100,000 — amounting to around 4 varicella deaths in children per year.[7] Risk factors for severe varicella include perinatal infection, immune compromise and adulthood (particularly in pregnancy). There is no known mechanism for the latter.

During primary infection, retrograde neuronal transport of virions along sensory nerves originating in the skin is believed to establish a reservoir of latent VZV in the dorsal root ganglia (DRG). Reactivation of this reservoir followed by anterograde neuronal transport causes herpes zoster: viral replication, pain and blistering lesions localized to the region of skin innervated by one or more adjacent sensory nerve roots (known as a dermatome). As for varicella, compromised immunity increases the incidence and severity of herpes zoster, as well as the risk of systemic dissemination.

VZV is a highly human-restricted pathogen, making *in vivo* models complex and expensive. Progress has been made with a humanized mouse model of VZV[2] and a non-human primate model of simian varicella virus.[3] Work in animal models has been complemented by the discovery of several genetic defects of the immune system in humans — reviewed here — that confer susceptibility to severe or recurrent VZV. We summarize how these data inform our understanding of human immunity to VZV; we also reflect on lessons learnt from vaccine development, closing with some suggestions for future work.

The concerted human immune response to VZV infection

The immune response to primary VZV infection was characterized in observational clinical studies in the 1980s.[9,10] Below we summarize the relative contributions of known innate and adaptive immune system mediators.

Interferon

Circulating type 1 interferon (IFN-α/β) increases as an initial response to VZV, and falls with resolution of disease.[10] There is also a significant influx into VZV skin lesions of plasmacytoid dendritic cells (pDC), which are specialized antigen presenting cells with a major role in the production of IFN-α/β.[11] Local release of IFN-α and activation of IFN-signaling molecules (e.g. STAT1, nuclear factor-κB (NF-κB)) occurs in VZV-infected human skin xenografts in mice with severe combined immunodeficiency (SCIDhu mouse).[4] In this model, blockade of IFN signaling with a neutralizing antibody to the IFN-α/β receptor increased both lesion size and skin VZV load (by approximately tenfold).[4] These findings are consistent with clinical observations that exogenous IFN-α can limit the severity of both varicella and herpes zoster in patients with cancer.[12,13] VZV has evolved multiple mechanisms to counter IFN-restriction, including inhibition of IRF3[14] and STAT1[15] phosphorylation and sequestration of the p50—p65 heterodimer of NF-κB in the cytoplasm of epithelial cells.[16] VZV infection of pDC *in vitro* also acts to inhibit the production of IFN-α/β by these cells.[11] The tempo of skin lesion formation in the SCIDhu mouse model, which lacks adaptive immunity, is similar to the clinical incubation period. These data support a containment role for IFN-α/β in the initial phases of VZV infection (Fig. 1).

The importance of IFN-α/β in innate defence against primary VZV seemed initially to be confirmed by the discovery of patients with extremely rare genetic defects in downstream components of IFN-α/β signaling, such as *TYK2*,[17] *STAT1*,[18,19] and NF-κB-essential modulator (*NEMO*).[20] In addition to viral susceptibility, these mutations predispose to intracellular pathogens such as mycobacteria (Duncan and Hambleton, *in press*) due to the broader defect in IFN-γ-IL12 signaling and the attendant effects on adaptive as well as innate immunity. However, susceptibility to severe virus infection was also recently reported in a group of individuals carrying an autosomal recessive mutation in *STAT2*.[21] STAT2 is a component of the heterotrimeric transcription factor ISGF3 that is formed downstream of the type I IFN receptor and activates the antiviral transcriptional program by binding to IFN-sensitive response elements (ISRE) in the promoter region of IFN-stimulated genes. The *STAT2* mutation severely attenuated the IFN-α/β antiviral response and produced marked susceptibility to viral infection of patient cells *in vitro*.[21] Despite confirmed VZV infection, however, these