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Viral Pathogenesis

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Glossary

Adaptive immunity The adaptive immune system is generally comprised of T and B lymphocytes which respond to specific molecular signatures (e.g., antigens or epitopes) on pathogens or other factors that are seen as nonself. The major components of the adaptive immune system are antibodies (produced by B cells), helper CD4 T cells, and cytotoxic CD8 T cells, all of which can contribute to viral control and clearance. In some instances, components of the adaptive immune system contribute to immune pathology.

Cytopathic effect In the context of viral infection, cytopathic effect refers to morphologic changes in cells that are brought about either directly or indirectly by viral infection. Cytopathic effect is often associated with cell killing due to direct effects of the viral infection.

Immune complex Aggregates of antigen (virus) and antibody that precipitate out of solution. When deposited into small blood vessels they can cause inflammation and tissue damage.

Immune evasion Avoiding or actively inhibiting components of the innate or adaptive immune system.

Immune pathology Tissue damage or disease that is due to the effects of the host immune system. This can involve direct tissue destruction as a result of immune-mediated viral clearance, where the immune response kills the virally infected cells, or indirect effects such as bystander tissue damage due to virus-induced inflammation or immune complex deposition in blood vessels.

Innate immunity Innate immunity encompasses a broad set of nonspecific immune processes that are rapidly induced following pathogen challenge. Innate immune components include, but are not limited to, the type I interferon system, the complement cascade, and natural killer (NK) cells. Though considered nonspecific, innate immune pathways are generally activated by danger signals, such as conserved pathogen associated molecular patterns (PAMPs), which are indicative of infection. Innate immune components mediate early control of pathogens, promote activation of the adaptive immune system, and also act as effector arms of the adaptive immune system.

PAMP Pathogen associated molecular patterns (PAMP) are molecules with conserved motifs that are associated with pathogen infection that serve as ligands for host pattern recognition molecules such as Toll-like receptors. PAMP interactions with pattern recognition molecules lead to activation of a wide array of innate immune pathways, thereby initiating early antiviral responses.

Pathogenesis The mechanisms that lead to diseases. In the context of viral pathogenesis, this describes a series of virus and host interactions at the cellular and systemic level that lead to virus-induced diseases.

Type I interferons Type I interferons (alpha/beta interferons) consist of a related set of cytokines that are released from cells in response to viral infection or virally derived components, such as double stranded RNA. All type I interferons bind to a conserved type I interferon receptor, where interferon receptor signaling leads to the induction of a large set of interferon-induced genes which possess direct antiviral effector function and immune regulatory activities.

Introduction

Viral pathogenesis is a term that generally describes the processes by which viral infection results in a disease. However, viruses can range from small RNA viruses (e.g., flaviviruses such as dengue virus) to large DNA viruses (e.g., herpesviruses and poxviruses), all of which interact with the host in unique ways to drive the virus-induced disease process. These virus specific disease outcomes are driven by fundamental differences in viral replication cycles, modes of transmission, tissue tropism, interactions with the host immune response, as well as a multitude of other variables. Furthermore, due to differences in a wide range of factors, including elements such as host genetic variation, host immune status, viral dose, or route of inoculation, infection with the same virus often results in varied disease outcomes in different individuals, where some individuals may develop no disease at all, while others are symptomatic and may develop serious or life threatening disease. Therefore, it is difficult to provide a general overview of viral pathogenesis that accurately encompasses the full range of virus-induced disease processes. However, while the pathogenesis of each virus and its associated disease(s) has unique aspects, it is also true that there are several common stages in the viral life cycle/disease process that are shared between all pathogenic viruses, and consideration of these common processes can be used to illustrate several key concepts in viral pathogenesis. For example, since viruses are obligate intracellular pathogens that are not capable of reproducing themselves outside of a permissive host cell, a virus must successfully gain entry to a target cell and propagate itself to cause a disease. Whether a virus can accomplish this task depends on interactions with key host molecules, such as cell surface receptors, which determine whether the virus can successfully infect and reproduce itself within its target cells. Therefore, for the purposes of this overview, we will consider several common virus/host interactions, including: (1) factors that affect viral

tissue tropism and host range, (2) viral immune evasion, and (3) viral effects on target cells or tissues. By focusing on these key steps in the viral life cycle/disease process, we can discuss some general concepts that illustrate how these interactions impact viral pathogenesis, while also emphasizing the virus specific aspects of these interactions that result in each virus-induced disease having unique attributes.

Viral Tissue Tropism and Host Range

As noted above, viruses cannot replicate outside of a permissive host cell, and gaining access to and being able to replicate within these cells represents a key part of any virus's life cycle. Furthermore, the induction of disease is usually dependent upon the effects of the virus on cells or organ systems that it infects, such as direct killing of essential host cells (e.g., neurons) by the virus (see below). Therefore, viruses that cannot gain access to and replicate within permissive host cells are generally not able to cause disease. Furthermore, viruses that cannot gain access to the specific tissue that is associated with a disease, such as the central nervous system for viruses that cause encephalitis, are also less likely to cause severe diseases. Though there are multiple virus–host interactions that determine whether a virus can successfully replicate within a target cell, for the purposes of brevity, we will consider specific examples of stages in the viral life cycle where interactions with the host determine whether the virus can successfully replicate in target cells, and how these interactions promote the virus-induced disease process Figure 1.

Receptor Interactions

Viral entry into host cells usually involves interactions between molecules on the surface of the virus and specific cell surface receptors, which allow the virus to bind to the host cell and initiate the viral entry process. In some cases, viruses interact with a single cell surface molecule, which mediates viral binding to the cell and also facilitates viral cell entry. For example, several rhinoviruses bind to ICAM-1 (CD54), and these interactions promote viral infection of the cell (reviewed in Rossmann et al., 2002). In contrast other viruses, such as herpes simplex virus, interact with cell surface molecules such as heparin sulfate to facilitate viral attachment to the cell, and then engage specific host receptor proteins on the cell surface that mediate viral entry into the cell (reviewed in Spear, 2004). Viral interactions with these receptors can have a significant impact upon several aspects of viral pathogenesis, including determining the cell or tissue tropism of a virus or even whether a virus can efficiently infect and cause disease in a specific host species.

The importance of virus–receptor interactions in disease pathogenesis is nicely illustrated by interactions between human immunodeficiency virus (HIV) and two host molecules, CD4 and CCR5, which mediate HIV binding and entry. HIV infection requires interactions between the viral gp120

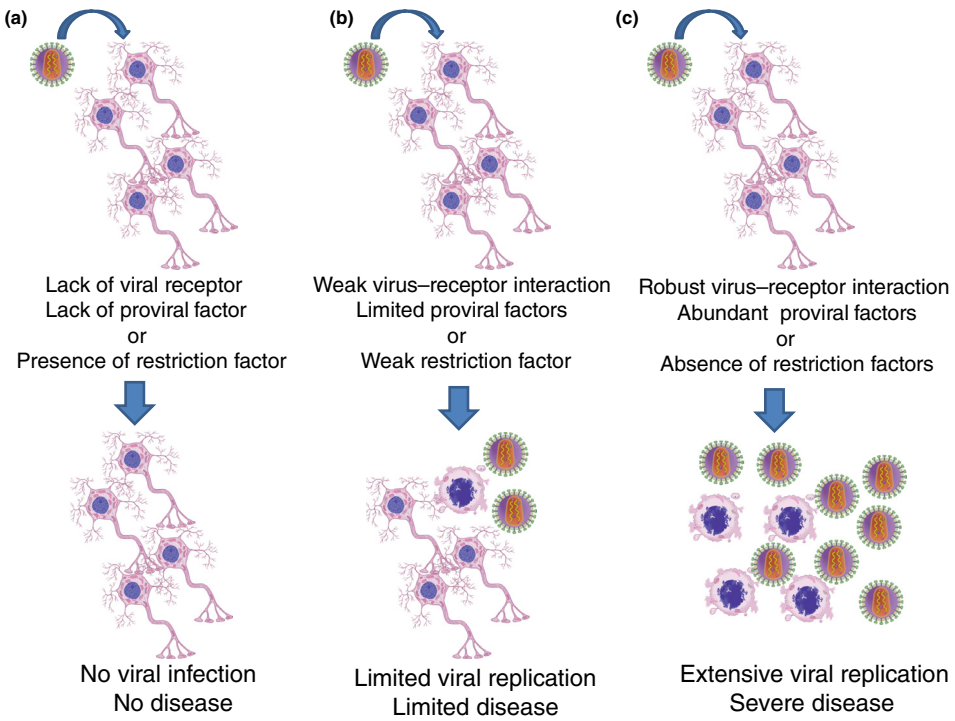

Figure 1 Strong receptor interactions, proviral factors, or host restriction factors can affect viral pathogenesis. (a) The absence of virus specific receptors or essential proviral factors, or the presence of strong antiviral restriction factors, can prevent viral replication and subsequent tissue destruction and disease development. (b) Weak receptor interactions, limiting amounts of proviral factors, or moderately effective restriction factors can result in limited levels of viral replication, poor viral spread, and mild tissue destruction or disease. (c) Strong virus–receptor interactions, abundant proviral factors, and the absence of antiviral restriction factors can result in high levels of viral replication, extensive virus-induced tissue destruction, and severe disease.

protein and CD4 (Sweet et al., 1991), a host protein expressed on a subset of T cells (CD4 positive helper T cells) and a limited number of other cell types, such as macrophages. Since HIV infection is dependent on interactions with CD4, CD4 positive helper T cells are the major target of HIV replication, and viral replication in these cells results in the progressive loss of CD4 T cells over the course of the HIV infection. CD4 T cells play an essential role in regulating the immune response, and HIV-mediated killing of these cells ultimately leads to immune suppression that leaves HIV infected individuals susceptible to lethal opportunistic infections that would normally be controlled by persons with fully functional immune systems. Therefore, viral interactions with CD4 and subsequent viral tropism for these cells, directly contributes to disease pathogenesis during HIV infection.

In addition to the importance of CD4 in determining HIV tropism, a second HIV/receptor interaction further illustrates the importance of receptors in driving viral pathogenesis. Following HIV gp120 binding to the CD4 molecule, the gp120 molecule undergoes a conformational change, which allows gp120 to interact with one of two coreceptor molecules, CCR5 or CXCR4, that then leads to viral fusion (Alkhatib et al., 1996; Feng et al., 1996). The importance of these interactions is illustrated by the fact that a small subset of humans has a nonfunctional form of CCR5, and these individuals are highly resistant to HIV infection (Liu et al., 1996; Dean et al., 1996; Huang et al., 1996). In other words, if the virus cannot get into its appropriate target cells through interactions with CCR5, it cannot efficiently infect these individuals and cause disease.

In addition to affecting disease pathogenesis by determining viral cell tropism, virus–receptor interactions can also broadly impact disease pathogenesis by determining whether a virus will efficiently infect a new host. This is particularly important for zoonotic viruses, which are viruses that naturally reside in animals, but which jump to humans and cause diseases. To successfully make the transition from its natural animal host to humans, a zoonotic virus must either interact with receptors that are highly conserved between species, or the virus must change (mutate) in a way that allows it to adapt to efficiently interact with receptors in the new host. An example of the first situation is provided by Sindbis virus, a mosquito-borne virus that must efficiently infect both mosquitos and vertebrate hosts. Recent studies have identified natural resistance-associated macrophage protein (NRAMP), as a receptor for Sindbis virus in both mosquitoes and vertebrate cells (e.g., humans) (Rose et al., 2011). NRAMP is highly conserved between species, and it is likely that by interacting with this highly conserved receptor protein, Sindbis virus is able to readily replicate in both mosquitoes and vertebrates. In contrast to situations where a virus interacts with a highly conserved receptor, there are also situations where the virus receptor is significantly different between species. Therefore, for the virus to successfully make the transition between the original animal host and humans, it is likely that the virus will have to adapt to more efficient use of the receptor in the new species. An example of this type of interaction is provided by the SARS coronavirus (SARS-CoV), which caused an outbreak of severe acute respiratory disease in 2002–03. SARS-CoV infects cells through interactions between the viral spike (S) protein and angiotensin converting enzyme-2 (ACE2) (Li et al., 2003). However, SARS-CoV is thought to normally reside in bats (Lau et al., 2005) and the bat-derived virus does not efficiently interact with human ACE2. However, studies suggest that mutations within the receptor binding domain of SARS led to more efficient interactions with the human ACE2 molecule, and that viruses with these adaptive mutations were better able to infect human cells (reviewed in Bolles et al., 2011; Graham and Baric, 2010). This is supported by the finding that introducing the region of the S protein that binds to human ACE2 into the bat SARS virus allows that virus to bind to human ACE2 and efficiently infect human cells (Becker et al., 2008). These results further reinforce the idea that virus receptor interactions play a crucial role in determining whether the virus can efficiently infect the host and ultimately cause disease.

Proviral Factors

Though receptor interactions represent a crucial component of virus–host interactions and viral pathogenesis, a number of other factors can also determine which tissues a virus infects. Most viruses encode their own replication machinery, however they are still dependent upon the host cell for a number of functions, including processes that promote viral entry or the translation and assembly of viral proteins. Recently, the field of virology has become very interested in identifying 'proviral' factors, which are host molecules that promote efficient viral replication. Identification of these proviral factors not only enhances our knowledge of how viruses interact with the host cell, but also may identify host pathways that could be targeted to inhibit viral replication and develop new therapies.

Many proviral factors are components of generally important cellular processes, such as the host translation machinery or cellular protein transport pathways, which are likely to be important for broad classes of viral pathogens. However, there are instances where host factors interact with specific viruses to enhance viral replication in specific cell types, thereby affecting both viral cell tropism and disease pathogenesis. In the most extreme examples, viral replication, and hence the ability to cause disease, would be severely compromised by the absence of a specific proviral factor. An excellent example of a virus-specific proviral factor is provided by hepatitis C virus (HCV) interactions with miR-122. HCV is a positive stranded RNA virus that infects the liver and causes chronic disease in a significant fraction of infected individuals, putting these individuals at risk for the development of chronic liver failure and the development of hepatocellular carcinoma (reviewed in Cabibbo et al., 2012). Though HCV may be able to replicate in cell types such as B and T cells, the major site of HCV replication are hepatocytes within the liver. A key determinant of HCV's tropism for hepatocytes is the host microRNA miR-122. MicroRNAs are small (20–22) nucleotide host RNAs, which regulate a number of biological processes within the host (reviewed in Szabo et al., 2012). In the context of HCV infection, miR-122 is expressed specifically within the liver and its expression enhances HCV RNA levels in hepatocyte cell lines (Jopling et al., 2005). Though the mechanisms of miR-122's actions on HCV are not completely understood, miR-122 interacts with RNA structures in the 5′ end of the viral genome, and these interactions are essential for miR-122's

effects on HCV (Jopling et al., 2005). The importance of these interactions for HCV replication and disease pathogenesis is illustrated by recent studies in a chimpanzee model of HCV where administration of a miR-122 specific antagonist resulted in decreased viral loads within the liver and a reduction in HCV associated disease signs within the liver (Lanford et al., 2010). Therefore, HCV interactions with miR-122 affect viral replication and disease pathogenesis within the liver, illustrating the potential importance of viral interactions with proviral host factors in promoting viral replication and driving the pathogenesis of virus-induced diseases.

Host Restriction Factors

It is important to note that in addition to proviral factors, there are also classes of host proteins that can act as restriction factors that actively inhibit a virus's ability to replicate and cause disease. These types of host restriction factors have been extensively studied in the context of retro/lentivirus infection and an excellent example of this type of factor is provided by TRIM5α. TRIM5α is part of a class of tripartite motif containing host proteins, a large number of which have been shown to exhibit antiviral or immune regulatory functions (reviewed in Mcnab et al., 2011). Studies looking at restriction factors that limit the ability of HIV to replicate in nonhuman primate cells found that the rhesus macaque TRIM5α molecule strongly interacts with the HIV capsid to block viral infection at an early stage in the viral replication process (Stremlau et al., 2004). In contrast, the human TRIM5α molecule, which interferes with retroviruses and lentiviruses such as equine infectious anemia virus, interacts less efficiently with HIV (Stremlau et al., 2005). Efficient interactions between TRIM5 and HIV appear to protect macaques from HIV replication and disease, while less efficient interactions between human TRIM5α and HIV in part explain the enhanced susceptibility of humans to HIV infection. Therefore, the presence or absence of appropriate restriction factors can have a major impact on host susceptibility to virus-induced disease, where the presence of a strong restriction factor would inhibit viral replication and prevent or limit virus-induced disease. In addition to TRIM5α, other factors that mediate host range restriction during lentivirus/retrovirus infection include APOBEC and tetherin (reviewed in Luban, 2012).

Viral Immune Evasion

The host innate and adaptive immune systems play a major role in protecting from virus-induced disease by limiting or preventing viral replication. The type I interferon system and other components of the innate immune response are rapidly activated in response to viral infection and play a crucial role in limiting viral replication and spread within the host. Likewise, components of the adaptive immune system, such as cytotoxic CD8 positive T cells and antibody, are involved in clearing virus from infected tissues and can provide long-term immunity to prevent reinfection. The complexity of the immune systems and its interactions with each viral pathogen is such that a comprehensive overview of virus–host immune interactions is beyond the scope of this article. However, though there are aspects of the virus–host immune interaction that are unique to each pathogenic virus, every viral pathogen must successfully avoid or actively antagonize the host immune response to infect, replicate, and disseminate within the host. In fact, viruses with defects in blocking the host immune response are often attenuated in their ability to cause disease. Therefore, immune evasion represents a common theme in viral pathogenesis that we will explore further. While different viruses employ a wide range of strategies to avoid/antagonize aspects of the innate and adaptive immune system, we will focus specifically on viral interactions with the innate immune system and the interferon response in particular to illustrate the importance of these interactions on viral pathogenesis.

Though multiple arms of the innate immune system contribute to viral control, including components such as the complement cascade, natural killer cells, and proinflammatory cytokines, several lines of evidence suggest that the type I interferon system plays an essential role in the pathogenesis of most viral pathogens. Most, if not all of the pathogenic viruses affecting humans either avoid or actively antagonize some aspect of the type I interferon response, and viruses that are defective for avoiding/antagonizing the type I interferon system are often attenuated for replication and disease in immunocompetent animals (Garcia-Sastre et al., 1998; Talon et al., 2000; Leib et al., 1999; Bouloy et al., 2001). Furthermore, animals lacking a functional type I interferon system exhibit enhanced sensitivity to a wide array of viral pathogens (Leib et al., 1999; Ryman et al., 2000; White et al., 2001; Bouloy et al., 2001; Schilte et al., 2010), which suggests that type I interferon (IFN) plays an essential role in limiting viral replication and protecting from disease.

The type I interferons are a group of cytokines consisting of a several related alpha interferon molecules and a single interferon beta protein, that are induced in response to stimuli associated with viral infections, such as double stranded RNA, and which bind to a common type I interferon receptor complex. Signaling via the type I interferon receptor leads to the induction of hundreds of interferon-stimulated genes (ISGs). Though the function of many of these ISGs still needs to be elucidated, it is clear that many of these molecules have antiviral activity against one or more viral pathogens (Schoggins and Rice, 2011), while some ISG molecules modulate other aspects of the host immune response, including antigen presentation (Schoggins and Rice, 2011). Therefore, the type I interferon system limits viral replication and dissemination by inducing an antiviral state within host cells, and then promotes viral clearance by modulating other aspects of the host immune response, including host antibody and T cell responses. For the purposes of this overview, we will briefly summarize several key aspects of the type I interferon response to illustrate how viruses can avoid or antagonize this response.

The production of type I interferon can be induced by signaling through several different pattern recognition molecules, including certain Toll-like receptors and cytoplasmic nucleic acid sensors, such as RIG-I. These pattern recognition molecules recognize pathogen associated molecular patterns (PAMPs), which are molecules that have signatures commonly associated with viral infection, such as double stranded RNA. Readers who are interested in more detailed discussion of the pattern recognition molecules that regulate the type I IFN

response are directed to the following reviews (Kawai and Akira, 2006; Nakhaei et al., 2009). Though simplified for this overview, following interactions with a viral PAMP, each pattern recognition receptor will activate a signaling cascade that ultimately converges on a set of transcription factors (IRF3 or IRF7), which upon activation, transit to the nucleus to induce type I IFN transcription and subsequent production of type I interferon. Type I interferons are secreted from the cell, and can then act in an autocrine (on the cell that produced the interferon) or a paracrine (affecting the surrounding cells) manner. The type I interferon receptor consists of two subunits IFNAR1 and IFNAR2, which upon interferon binding, dimerize at the cell surface. The receptors are associated with two protein tyrosine kinases, Janus activated kinase 1 (Jak1) and tyrosine kinase 2 (Tyk2), that are brought together during receptor dimerization. Jak1 and Tyk2 then undergo auto- and/or transphosphorylation (de Weerd et al., 2007; de Weerd and Nguyen, 2012), which leads to their activation, and they in turn phosphorylate tyrosine residues present on the receptor tails that serve as docking sites for signal transducers and activators of transcription (STAT) factors. Jak1 and Tyk2 phosphorylate STAT1 and STAT2, which then form heterodimers and interact with interferon regulatory factor 9 (IRF9), where this complex localizes to the nucleus and binds promoters containing IFN-stimulated response elements to drive expression of ISGs, which mediate direct antiviral effector functions and modulate the host immune response (Kawai and Akira, 2006; Nakhaei et al., 2009; deWeerd, 2012). Importantly, though there are instances of viruses avoiding or antagonizing specific antiviral effector molecules (Daffis et al., 2010), the majority of known viral interferon evasion strategies are directed at either avoiding recognition by host pattern recognition molecules or targeting the signaling pathways associated with either type I interferon induction or interferon receptor signaling. Therefore, we will briefly discuss a few examples of interferon antagonism to illustrate the importance of these interactions in viral pathogenesis.

A number of viruses antagonize type I interferon induction either by targeting specific components of the interferon induction pathways or by broadly inhibiting *de novo* RNA synthesis/protein translation in the infected cell, which effectively blocks the production of type I interferon. One strategy for avoiding type I interferon induction is to shield viral PAMPs (e.g., viral RNA) from recognition by host RNA sensors, such as RIG-I and Mda5. A number of viruses encode RNA binding proteins that have been shown to inhibit type I IFN induction. For example, the ns1 protein of influenza A virus, which interferes with type I IFN induction at several stages in the induction process, exhibits potent antagonist activity against type I interferon induction, and this antagonism is in part due to RNA binding activity by ns1 (Donelan et al., 2003). Another example of this type of strategy is provided by the nucleocapsid protein (N) of the SARS coronavirus, which also inhibits type I interferon induction at an early stage in the RNA recognition process, and this inhibitory activity is dependent upon the RNA binding activity of the N protein (Lu et al., 2011). In addition to blocking host recognition, a wide array of viruses encode proteins that block specific components of the type I interferon signaling cascade. For example, the influenza A virus ns1 protein, in addition to shielding the viral RNA from recognition, prevents RIG-I activation and interferon induction in response to influenza infection by blocking the function of TRIM25, a ubiquitin ligase that regulates the activation of the RNA sensor, RIG-I (Gack et al., 2009), while a second viral protein, PB1-F2 interferes with type I interferon induction through interactions with MAVS, an adaptor molecule that is essential for RIG-I-mediated type I interferon induction (Conenello et al., 2011; Varga et al., 2011). The fact that influenza virus employs multiple strategies to block type I interferon induction argues that viral interactions with the type I interferon system are particularly important in regulating viral replication, and this is further supported by the fact that viruses with mutations in either ns1 or PB1-F2 induce higher levels of type I interferon and are subsequently attenuated in their ability to cause disease (Conenello et al., 2011; Donelan et al., 2003). Therefore, viruses that are defective in their ability to antagonize the host type I interferon system are often unable to replicate and spread efficiently within the host, illustrating the importance of viral immune evasion strategies in determining whether a virus will be pathogenic (**Figure 2**).

In addition to blocking type I interferon induction, a number of viruses also interfere with type I interferon receptor signaling, since this effectively blocks the induction of antiviral ISGs. For example, the type I interferon signaling pathway is targeted at multiple stages by members of the flavivirus family, with multiple proteins from the same virus often targeting different steps of the pathway (reviewed in Diamond, 2009), again illustrating the importance of interferon antagonism for viral success. As is the case with antagonism of type I interferon induction, viral interactions with the type I interferon signaling pathways are likely to have a major impact on virus-induced disease. Studies with reovirus have shown the induction of virus-induced myocarditis is associated with suppression of type I interferon receptor signaling, where the viral M1 gene from a myocarditic virus exhibits enhanced ability to interfere with the IRF9 component of the ISGF3 signaling complex (Zurney et al., 2009). These results suggest that viral antagonism on interferon receptor signaling can have a major impact on the pathogenesis of virus-induced disease, and that differences in the efficiency of interferon antagonism between related viruses can have significant impacts on what types of disease those viruses cause.

Viral Interactions with Target Cells and Tissues

As noted above, viruses are obligate intracellular pathogens that cannot reproduce themselves outside of host cells. Therefore, the types of cells that a virus targets and what effect the virus infection has on a target cell plays a major role in determining whether a virus will induce disease and if so, what type of disease the virus causes. Most simply, some viruses are cytopathic, in that the virus infection results in direct killing of the host cell, while other viruses are noncytopathic and do not directly kill the infected cell. However, while some viruses cause disease due to their targeting and killing of essential cell types, such as neurons, the mechanisms leading to virus-induced disease are often complex and we will discuss some examples of different interactions between viruses and host cells or the host immune response that affects disease outcomes (**Figure 3**).

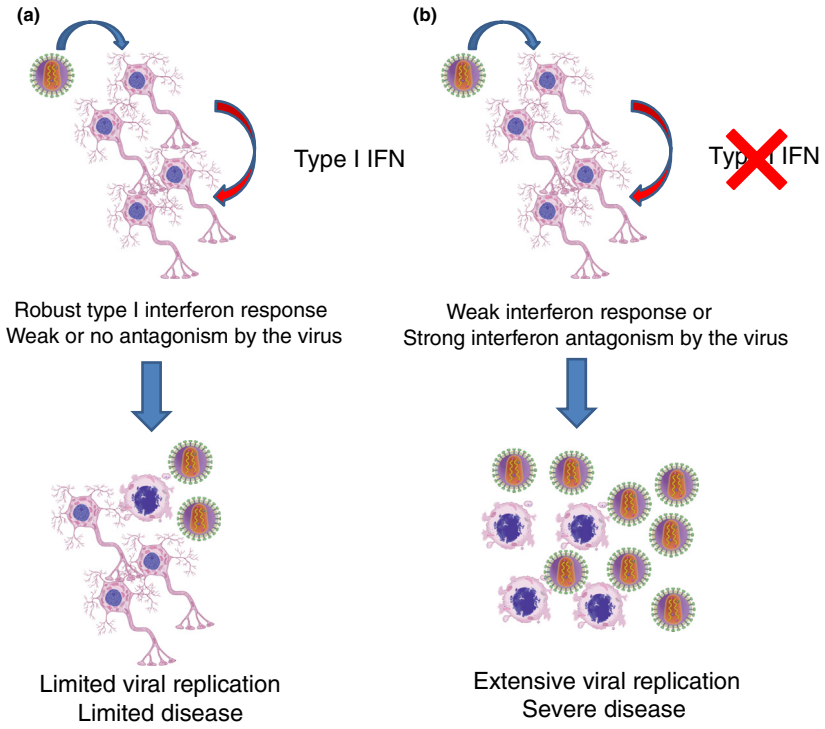

Figure 2 Type I interferon antagonism can impact viral pathogenesis. (a) In the presence of a robust type I interferon response, and the absence of effective viral interferon antagonism, type I interferon will induce an antiviral state that limits viral replication and spread, thereby limiting virus-induced disease. (b) If the virus effectively interferes with the type I interferon response, interferon will be prevented from inducing a robust antiviral state within the host, and the virus is able to replicate to higher levels, will spread more efficiently, and may cause more severe disease.

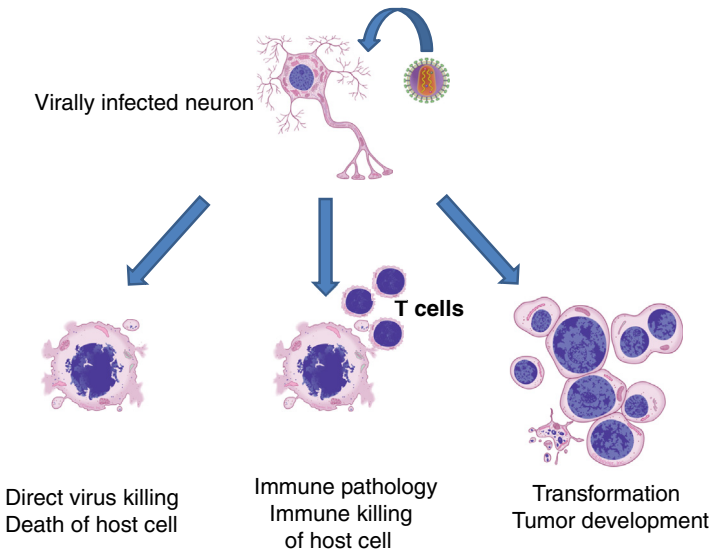

Figure 3 Examples of pathologic outcomes of viral interactions with host cells and tissues. Direct virus-induced cell killing: viral infection may lead to direct killing of host cells, resulting in the loss of essential cell types, which can directly contribute to disease. Virus-induced immune pathology: the host immune response to the virus may lead to direct killing of the infected cells, or bystander killing of uninfected cells, resulting in tissue destruction, which can lead to the development of disease. Viral transformation: viral infection may lead to the transformation of infected cells, ultimately resulting in the development of cancer.

Direct Virus Killing

A number of viruses are directly cytotoxic and productive viral replication leads to direct cell killing. Therefore, if the cell type that these viruses replicate in is essential, such as neurons, virus-induced killing of these cells can directly lead to disease. A number of viruses, including alphaviruses such as Sindbis virus and Venezuelan equine encephalitis virus (VEE), cause direct killing of host cells. While the mechanisms leading to cell death are not completely worked out, it is generally accepted that these viruses induce apoptotic cell death in infected cells (Ubol et al., 1994; Griffin et al., 1994). Since these viruses exhibit strong tropism for neurons, viral replication within the central nervous system leads to neuron death and degradation of neurologic function. Though there is evidence that the host immune response exacerbates virus induced disease during both Sindbis virus and VEE infection (Rowell and Griffin, 2002; Kimura and Griffin, 2003; Charles et al., 2001), in the case of VEE, mice lacking a functional adaptive immune system still succumb to virus-induced disease (Charles et al., 2001), suggesting the direct cell killing by the virus contributes to disease pathogenesis.

Virus-Induced Immune Pathology

The host immune systems plays a crucial role by protecting from virus-induced disease, however there are clear instances where an overactive or inappropriate host immune response contributes to the pathogenesis of virus-induced disease. This is perhaps most clearly illustrated in situations where a virus is noncytopathic and does not cause the direct death of infected host cells, yet viral infection still results in tissue destruction and disease. Hepatitis B virus (HBV), which causes serious acute and chronic hepatitis in infected humans, nicely represents this situation and also illustrated both the importance of the host immune system in promoting viral clearance and the potential for ineffective or overly active immune responses to potentiate virus-induced disease. In most immunocompetent individuals, HBV infection causes acute hepatitis, where the host immune response plays an essential role in viral clearance, but in the process, also causes some liver injury (Chisari et al., 2010). HBV is noncytopathic for hepatocytes and during the early stages of HBV infection there are no signs of liver disease, even though the virus is replicating to high levels within the liver (Chisari et al., 2010). It is only after the host adaptive immune response has started to clear the virus from the liver that signs of liver injury are evidence, which suggests that though beneficial in clearing the virus, aspects of this immune response are pathologic. Through the use of transgenic mouse models and HBV infection of chimpanzees, it has been shown the virus specific CD8 T cells are responsible for both the clearance of the virus from the liver and are the mediators of the acute liver injury associated with HBV infection (Thimme et al., 2003). Immune interactions also play a major role in the pathogenesis of chronic HBV infection, where chronic disease is associated with a weak HBV specific CD8 T cell response that is unable to clear the infection (Chisari et al., 2010). Furthermore, evidence from HBV transgenic mouse models suggests that suboptimal CD8 T cells responses that fail to clear HBV infection may be associated with chronic liver inflammation and damage that ultimately leads to the development of hepatocellular carcinoma (Chisari et al., 2010).

Immune pathology is not restricted to infection by noncytopathic viruses, and overactive or inappropriate immune responses are thought to contribute to disease even when the virus itself is capable of causing direct cell killing. As noted above, even though Sindbis virus and VEE are thought to directly contribute to virus-induced neurologic disease by killing neurons, it is also clear that components of the host adaptive immune response can exacerbate the disease process with these viruses (Charles et al., 2001; Rowell and Griffin, 2002; Kimura and Griffin, 2003). This concept is also illustrated by Ross River virus (RRV), another alphavirus that is associated with severe arthralgia and myalgia in infected humans. Studies in humans and mouse models have shown that RRV replicates to high levels in joint and muscle tissues and that viral replication within these tissues leads to the development of arthritis and myositis (Aaskov et al., 1985; Hazelton et al., 1985; Morrison et al., 2006). Further analysis found that even though RRV is cytopathic, depletion of macrophages significantly reduced the severity of virus-induced disease, suggesting that components of the inflammatory response, rather than direct virus-induced killing, are responsible for virus-induced disease (Lidbury et al., 2000). Furthermore, activation of specific components of the host complement cascade, including mannose binding lectin and the C3 component of complement, are associated with severe RRV-induced disease in humans and mice lacking either of these factors are highly resistant to virus-induced disease (Morrison et al., 2007; Gunn et al., 2012).

It is also important to remember that while the above examples focus on instances where components of the immune response directly contribute to cell killing in virally infected tissues, immune-mediated pathology may not always be restricted to direct effects on virally infected cells or within virally infected tissues. A number of chronic viral infections, including hepatitis C virus (HCV) infection, are associated with the development of immune complexes, where aggregates of virus and antibodies precipitate within small blood vessels and lead to the development of inflammation (vasculitis) (reviewed in Lauletta et al., 2012). Therefore, while generally beneficial, there are instances where overactive or inappropriately activated components of the antiviral host immune response directly contribute to the pathogenesis of virus-induced disease. Since there is significant person to person variation in immune function, variation in the magnitude and composition of the host immune response may play a major role in determining whether an individual mounts an immunopathologic immune response and thereby develops disease.

Virus–Cell Interactions and Cancer

Not all pathologic interactions between viruses and their target cells/tissues involve direct cell killing and tissue damage, and virus-induced cancer is a serious consequence of some viral infections. While cancers associated with some viral infections are due to indirect effects such as immune suppression associated with HIV infection or chronic inflammation associated with HBV or HCV infection (see above), there are also examples of situations where viral infection directly promotes tumor

development. Several gamma herpes viruses, including the human gamma herpes viruses, Epstein Barr virus (EBV) and Kaposi sarcoma-associated herpesvirus (KSHV), are associated with lymphoproliferative disorders and cancer in humans. Both of these viruses encode a number of proteins, such as EBV EBNA2 and LMP1 or KSHV LANA-1 and v-cyclin that are associated with cellular transformation and cancer (reviewed in Cesarman, 2011). Likewise, human papilloma viruses (HPV), which can cause several types of cancer, including cervical cancer, encode several proteins, including viral E6 and E7 proteins, that interfere with cell cycle progression checkpoints and promote cellular transformation (Korzeniewski et al., 2011). Though infection with any of these viruses has the potential to cause cancer, as is the case with most aspects of viral pathogenesis, there are multiple additional factors that determine whether an individual is at risk for development of disease. In the case of EBV, since the viral proteins are recognized by the host immune response, individuals with healthy immune systems are at much lower risk of developing EBV associated cancers (reviewed in Cesarman, 2011). Likewise, in the case of HPV infection, there are multiple HPV genotypes and the risk of developing HPV associated cervical carcinoma is much greater with certain high risk HPVs, such as HPV 16 or 18 (Korzeniewski et al., 2011). Therefore, like other aspects of viral pathogenesis, a complex series of virus–host interactions determines whether infection with cancer associated viruses ultimately results in disease development.

Summary

Viral pathogenesis represents a complex series of interactions between viruses and the host that determine whether the virus will successfully establish infection within the host and if so, whether this infection will result in virus-induced disease. As discussed above, though the pathogenesis of each virus is unique, there are several stages in the viral life cycle that are shared by all pathogenic viruses which illustrate common themes in viral pathogenesis. However, it is important to remember, that within each of these common stages, there is tremendous variation in how each virus interacts with the host, and that these complex interactions are ultimately what determine whether a viral infection results in disease.

See also: Epstein–Barr Virus; Hepatitis Viruses; Human Immunodeficiency Virus Type-1; Influenza Virus Infections; Kaposi's Sarcoma-Associated Herpesvirus: Biology of a Human Tumor Virus; Papillomaviruses; Picornaviruses: Pathogenesis and Molecular Biology; Viruses and MicroRNAs.

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