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Pathology and Pathogenesis of Virus Infections

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INTRODUCTION TO VIRUS-INDUCED TISSUE DAMAGE

Viruses, as obligate intracellular parasites, pose a unique challenge to the host immune system, as a balance between clearance of the invader and collateral damage to host tissues must be met to ensure survival of the host as a whole. While overall, the immune response to viral infection is protective and balance is achieved, both inadequate and overactive immune responses can result in pathology. An overly intense immune response may clear the virus at the expense of the tissues surrounding the site of replication, resulting in damage and lesions caused by immunopathology; a prime example of this (discussed later in the chapter) is the inflammatory response induced by respiratory syncytial virus in the lungs. In contrast, insufficient responses to a viral infection can permit the virus to induce excessive direct tissue damage upon acute or persistent infection (as in herpes viral infections). Persistent infections can cause pathology resulting from chronic direct effects of the virus on the infected cell (many times this can be in the development of cancers, for example, in HCV infection) as well as the burden of persistent activation on the immune system (for example, in HIV infection).

A multitude of factors contribute to inadequate clearance of viral invaders resulting in persistent or chronic infections. Diverse cell type and tissue tropism can lead to the widespread distribution of virus within the host. Such seeding can provide an endless number of reservoirs for the virus, making clearance a futile task (for example, HIV can hide in antigen-presenting cells and in the central nervous system). In addition, the ability of a virus to go latent or to spread directly from cell to cell, avoiding a prolonged extracellular or viremic phase of infection, can serve as an effective immune evasion strategy, thus limiting exposure of the virus to immune effectors. Cell-to-cell spread and latency are two strategies employed widely by herpesviruses to evade direct detection. Virus-induced immunomodulation (both disruption of the innate and adaptive arms) represents yet another mechanism by which some virus families are able to promote a long-term association with the host. For example,

the human cytomegalovirus genome encodes a vast number of viral gene products known to disrupt both the adaptive and innate immune response to viral infection and, as such, is able to maintain a lifelong association with the host. Likewise, a number of different host factors, which contribute to inadequate viral clearance, include deficits in antigen presentation or immune effector cell trafficking and activation. Manipulation of the aforementioned effector mechanisms, as seen in the Clone 13 strain of LCMV (lymphocytic choriomeningitis virus), contributes significantly to the persistence of a multitude of viruses. In addition, feedback loops that are in place to dampen the acute immune response to minimize tissue damage by antiviral effector cells, can allow virus to escape eradication from the host if they shut off the immune response prematurely, resulting in the establishment of a persistent or latent viral infection.

Virus-induced pathology can thus be the direct result of a lytic viral infection or a consequence of immune activation, and therefore is the result of both host and viral contributions. Viruses whose replication cycle can culminate in cell lysis are not always lytic for all infected cell types. Additionally, host components may also determine the degree of virus-induced apoptotic cell death. Nonlytic viruses can be well adapted to their natural host, for example by becoming latent or by evading the host's immune response (herpes viruses are a good example for this). Lesser symptoms during the acute infection allow the host to better tolerate the infection, thus providing greater opportunity to spread to reservoirs within the host and to spread to a new host. While some of these "smoldering" infections can be benign in the healthy immunocompetent host, the constant or serial activation of the immune system to such infections can present with significant pathology in the immunocompromised host. Lastly, differences in the pathogenicity of viruses are often determined by the cells or tissues that are permissive for virus replication. Targeting of more sensitive organ systems, as is the case for influenza (lungs) and hepatitis (liver) viruses, can lead to serious disruption of normal cell and system function, resulting in pathology associated with diminished organ function.

Overall, all forms of virus-induced tissue damage involve virus factors as well as host factors and therefore, understanding the relationship between the virus and its host is essential to the development of effective interventions (Table 1).

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TABLE 1 Examples of host and viral factors contributing to virus induced pathology

Type of pathology	Host factors contributing ^a	Viral factors contributing	Associated virus(es)
Cytolysis	Inadequate IFN response; robust CTL response; susceptible cell type	Lytic viral egress	Common to many viruses including Epstein-Barr virus (B cells), human papillomavirus
Apoptosis	Cytokines can induce bystander apoptosis as well as infected-cell apoptosis	Presence of dsRNA; viral blockade of host protein synthesis	Common to many viruses including bunyaviruses, flaviviruses, adenoviruses, Sindbis virus
Allergic response	Development of IgE; Th2-biased response to virus; possible genetic predisposition has been suggested	High infectivity, cytopathology; viral inhibition of interferon response	Respiratory syncytial virus
Th17	Elevated IL-17 production; TNF α /IFN γ imbalance; disruption of Fas-FasL signaling	Unknown	Theiler murine encephalitis virus
Cytokine storm	Excessive inflammatory cytokine production, particularly TNF α	Down regulation of early type I IFN	Sin nombre virus, dengue virus, poxviruses
Immune complex formation	Induction of complement cascade and incomplete clearance of virus-Ab complexes	Viremic, extracellular stage of life cycle; prolonged association with host	Lymphocytic choriomeningitis virus, hepatitis B virus
Antibody dependent enhancement of infection	Generation of nonneutralizing Ab; susceptibility of Fc receptor-bearing cells to infection	Secondary infection with heterologous serotype (DHV)	Dengue hemorrhagic fever virus, human immunodeficiency virus, Ebola virus

^a IFN, interferon; CTL, cytotoxic T lymphocyte; IL, interleukin; TNF, tumor necrosis factor.

VIRUS-INDUCED IMMUNOPATHOLOGY

In addition to the direct effects of virus infection on the host cell, the potential of the immune system to respond to the invasion in itself is often the source of pathology (immunopathology). While the term immunopathology was originally used to describe an aberrant immune response to autoantigen resulting in pathology, more recent developments in our understanding of virus-induced immunopathology have revealed that this can be linked to both an aberrant immune response to the virus itself as well as unfavorable virus-induced changes to the immune response as a whole; for example, lymphopenia following certain types of infections as well as the specific loss of CD4 T cells in HIV infection. Today, advancement in available tools and techniques allows us to more precisely distinguish between pathology directly linked to virus infection of the target cell or, alternatively, as a consequence of the response to the infection by the host immune system.

Viruses have been demonstrated to induce immune cell dysfunction through a variety of mechanisms, including direct infection of immune effector cells and indirect means, which impact immune cell function. Direct effects of virus infection include situations where infection ultimately leads to the death of the cell be it through the induction of apoptosis, killing by immune effectors, or cytolytic infection.

Additionally, lymphotropic viruses can directly induce immunopathology through the infection of immune effectors and virally encoded immunomodulatory proteins. Herpesviruses are classic examples of virus-induced immunomodulation and represent a vast area of research, and, as such, this topic will be addressed in a separate chapter. Additional examples of virus-induced pathology include the induction of apoptosis, tissue damage resulting from oxidative burst, complement cascade, and a host of other mechanisms.

T-CELL MEDIATED CYTOLYSIS AND INDUCTION OF APOPTOSIS

Perhaps the most common virus-induced pathology is T-cell-induced destruction of host tissues. T-cell mediated

pathologies occur through both direct and indirect mechanisms including the targeted cytolysis of the infected cell by effector T cells, the induction of apoptosis in infected cells and generalized tissue damage due to bystander effects of T-cell activation. Overt pathology associated with T-cell effector functions is seen primarily in cases in which the offending pathogen is noncytolytic and where the T-cell response, not the direct effects of viral infection, induces the majority of the damage, as is the case with chronic herpes simplex virus-induced stromal keratitis (HSK).

More than 400,000 individuals in the United States suffer from ocular herpes simplex infections, one of the leading causes of infectious blindness (Pepose, 1996). HSV-1 infection of the corneal epithelium leads to the infiltration of large numbers of inflammatory cells (including neutrophils, CD4 and CD8 T cells, macrophages, dendritic cells, and natural killer cells) into the cornea and the secretion of proinflammatory cytokines and chemokines, all culminating in tissue damage (Banerjee et al., 2004; Deshpande et al., 2004; Deshpande et al., 2001; Pepose et al., 1985; Thomas et al., 1997; Youinou et al., 1986; Youinou et al., 1985). It is estimated that 20% of acutely infected individuals go on to develop HSK, a chronic lesion of the corneal stroma, characterized by corneal ulceration and necrosis, neovascularization, and stromal edema (Liesegang, 2001; Streilein et al., 1997). Scarring of the cornea leads to opacity and can culminate in blindness.

Two forms of HSV-induced stromal keratitis have been described in the literature: necrotizing stromal keratitis (NSK) and immune stromal keratitis (ISK). NSK is commonly associated with acute viral infection and characterized by the presence of viral antigen and intact virions in the corneal keratocytes, epithelial cells, and endothelial cells (Deshpande et al., 2004; Metcalf & Kaufman, 1976). The finding of intact virions in the cornea suggests that an active infection may directly mediate the damage to the cornea seen in NSK. Further evidence in support of the direct effects of virus in acute epithelial keratitis NSK can be found in the efficacy of antiviral treatment in alleviating

the symptoms of NSK (Deshpande et al., 2004; Kaufman, 2002). This is in contrast to immune stromal keratitis where viral antigen is no longer detected in the chronic lesion and disease is largely attributed to immunopathology.

Mounting evidence supports an immunopathological origin in chronic HSK pathogenesis. While viral loads tend to be elevated in primary acute infection, HSK pathogenesis is relatively rare in previously naïve patients, but more commonly seen in secondary infection/reactivation from latency (PePOSE, 1996). The observation that secondary infection is more commonly associated with HSK suggests that a primed preexisting adaptive immune response likely plays a role in disease. Furthermore, the use of immunosuppressive steroid therapy to treat chronic HSK, coupled with the exceptionally low incidence of HSK in immunodeficient patients as compared to immunocompetent individuals all implicate the immune response in disease progression (Liesegang, 1999).

A role for T-cell mediated pathogenesis is specifically supported by a series of elegant experiments utilizing adoptive transfer of either HSV-reactive CD8 or CD4 T cells into infected mice (Banerjee et al., 2005; Metcalf & Kaufman, 1976; Shimeld et al., 1989). These studies demonstrated that while HSV reactive CD8 T cells enter the cornea during the acute phase of infection, it is the CD4 T cells that predominate in the chronic phase. Further investigation into the contribution of both CD4 and CD8 T cells demonstrated that the early infiltration of HSV-reactive CD8 T cells into the cornea mediated protective clearance of the virus and was not involved in the development of corneal lesions. Later infiltration of HSV-reactive CD4 T cells, during the chronic phase where viral antigen is undetectable by current methods, was found to mediate HSK pathogenesis. The observation that HSK progresses in the absence of detectable viral antigen is addressed in the bystander activation hypothesis, which proposes that initial recognition of viral antigen by CD4 T cells results in a downstream cascade of inflammatory events culminating in the subsequent TCR independent activation of memory T cells (Banerjee et al., 2002; Deshpande et al., 2001; Gangappa et al., 1998). While T cells have been widely implicated in disease progression, HSK pathogenesis involves a complex cascade of events and, as such, there are likely multiple mechanisms of virus-induced immunopathology at play in HSK.

VIRUS-INDUCED ALLERGIC RESPONSE

Early childhood infection with respiratory syncytial virus (RSV), a noncytopathic virus associated with lower respiratory tract disease in infants, is a widely recognized risk factor for the development of childhood asthma and wheezing (Martinez, 2003; Perez-Yarza et al., 2007). RSV induced respiratory distress bears a number of similarities to allergic airway hypersensitivity response (AHR) including excessive mucus secretion, elevated levels of IgE antibody, and a sizeable infiltration of eosinophils into the lungs.

While a direct cause-and-effect relationship between RSV infection and the development of subsequent AHR has yet to be demonstrated, several observations strongly suggest a link between the two. In particular, recent studies implicate the propensity of the host to initiate a Th2 biased response to the primary RSV infection as a factor in the development of an allergic-type reaction to subsequent exposures to the virus. In a mouse model of RSV induced AHR, Th2 cytokines, IL4 and IL13, were found to be required for virus-specific IgE production and subsequent AHR development. In the context of allergic responses to foreign antigen in the airway, IgE bound to its cognate antigen

binds to FcεR1s on the surface of mast cells, triggering the degranulation of mast cells. While the role of *allergic* IgE in the alteration of airway function is well understood, relatively little is known about the role of *virus-specific* IgE in airway remodeling and anti-viral host defense. A recent study found that while neutralization of anti-RSV IgE antibodies blocked the development of AHR, neutralization did not impact viral titers in the lungs, suggesting that one, viral replication alone does not cause disease and two, the IgE response is not effective in controlling viral clearance and thus may prove to be useful as a therapeutic target (Dakhama et al., 2009).

VIRALLY INDUCED TH17 MEDIATED PATHOLOGY

In addition to pathology mediated by Th1 and Th2 responses, other effector cytokines, such as IL-17 (interleukin-17) is secreted by so-called Th17 cells, although it has yet to be shown that these constitute a separate lineage, have also been implicated in virus-induced immune mediated tissue damage. Th17 cells are a subset of CD4 T cells, which express IL-17. Although they have been demonstrated to play a protective role in defending against extracellular bacterial and fungal infections, they have also been associated with inflammatory tissue damage and several autoimmune disorders (Bettelli et al., 2008, 2007; Dong, 2008; Park et al., 2005). While up regulation of IL-17 has been described for several viruses including HIV, HSV, and RSV only recently have studies utilizing the Theiler's murine encephalomyelitis virus (TMEV) multiple sclerosis model revealed a novel role for Th17 cells in the promotion of chronic virus infection (Hou et al., 2009). Multiple sclerosis (MS) is a disease characterized by the destruction of the protective myelin sheath enveloping the neuronal axons of afflicted persons. Although generally believed to be an autoimmune disorder, the factors contributing to the initiation of MS remain an area of hot debate. Murine infection with TMEV has been used to model the hypothesis that viral infection may provide the trigger initiating an autoimmune cascade. Th17 polarization and subsequent IL-17 production in the TMEV infection model was found to promote the survival of infected cells by both inhibiting apoptosis of infected cells and rendering target cells resistant to killing by effector T cells. While IL-17 treatment of CD8 T cells did not significantly alter the frequency of granzyme B and IFN-γ (interferon-gamma) positive cells, treatment did render the target cell resistant to Fas-FasL-mediated killing by effector T cells. Ultimately Th17 polarization promotes persistence of the virus and subsequent pathology associated with chronic demyelination.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

Systemic inflammatory response syndrome, commonly referred to as a cytokine storm, results from an overproduction or systemic release of inflammatory cytokines (Flint, 2004). Under normal circumstances, the inflammatory response aids in the mobilization of primary effector cells of both the innate and adaptive arms of the immune response. Increased vascular barrier permeability and the localized release of cytokines direct immune cell traffic toward the site of primary infection and facilitate pathogen clearance. However, virus-induced cytokine dysregulation resulting in an overabundance of inflammatory cytokines can induce a shock-like syndrome where excessive edema, as well as cytokine and effector-cell-induced tissue damage, can lead to overall tissue destruction and subsequent organ failure. While the

precise events triggering the disproportionate inflammatory response to viral infection are not well understood, both host and pathogen factors are believed to play a role in this potentially fatal immune response.

Virus-induced cytokine storms have been implicated as the primary cause of disease in a number of viral infections, including certain types of hantaviruses. The first documented cases of hantavirus pulmonary syndrome (HPS) occurred in 1993 in the Four Corners region of the southwestern United States and resulted in a 40% case fatality rate, primarily afflicting young and otherwise healthy individuals. HPS is characterized by capillary leakage in the lungs, resulting in an acute respiratory distress syndrome, thrombocytopenia, and cardiac shock. The causative agent was later identified as a newly emergent hantavirus, later named *Sin Nombre virus* (SNV). Some years later another hantavirus, the Andes virus, inducing an HPS-like syndrome, emerged in South America. Difficulties in establishing an animal model of HPS had greatly hampered progress in understanding the factors involved in pathogenesis. However, the emergence of Andes virus opened up new avenues of research as infection of the Syrian hamster, a small animal model previously used for hantavirus vaccine strategies, for the first time reproduced a Hanta-induced HPS-like pathology, facilitating the study not only of infection, but pathogenesis as well.

HPS appears to have both viral and host genetic components as illustrated in the Syrian hamster model of Hanta-induced HPS. Both SNV and Andes virus are able to productively infect both humans and Syrian hamsters. However, while both are capable of inducing HPS in humans, only Andes virus can trigger HPS in Syrian hamsters (Abel Borges & Figueiredo, 2008; Saggiaro et al., 2007). Although to date a specific host factor has yet to be identified, one potential virion component of HPS has; sequence differences in the G1 viral glycoprotein lead to proteasomal degradation in pathogenic strains, whereas nonpathogenic strains remain stable (Sen et al., 2007). This difference in viral glycoprotein tail stability is hypothesized to lead to increased antigen presentation and CTL activation thus contributing to Hanta-induced immunopathology.

IMMUNE COMPLEX FORMATION

Antiviral antibodies can bind whole virus or processed viral antigen on the surface of infected cells, resulting in virus-antibody (V-Ab) immune complex formation. The generation of V-Ab complexes triggers a cascade of downstream events with both protective and pathological potential. Circulating V-Ab immune complex can be cleared through the activation of the complement cascade, culminating in the binding of complement components on the surface of erythrocytes (Janeway, 2001). V-Ab complexes bound to erythrocytes are then transported to the spleen and liver where macrophages remove the V-Ab complex from the surface of the erythrocyte and subsequently degrade the virus-Ab-complement complex, thus clearing the pathogen. However, effective clearance of immune complexes is not always achieved, particularly in the case of chronic viral infection. Immune complexes that are not cleared by phagocytes are deposited in the basement membranes of small blood vessels. Extensive tissue damage due to the deposition of V-Ab-complement complexes is a primary etiology for renal dysfunction associated with viral infection. Such cases of disease associated with immune complex deposition were first described with chronic LCMV infection, and later identified in hepatitis B virus infections of humans (Buchmeier & Oldstone, 1978; Oldstone & Dixon, 1969).

ANTIBODY-DEPENDENT ENHANCEMENT OF INFECTION

In addition to tissue damage arising from immune complex deposition in the small vessels, the formation of antibody-virus complexes can augment viral infection of Fc receptor bearing cells. While Fc receptors expressed on cells such as macrophages, dendritic cells, B cells, mast cells, and natural killer cells cannot substitute for the endogenous viral receptor; they have been demonstrated to act as coreceptors, capable of enhancing infection of antigen presenting cells (APCs).

While the precise mechanism of action is still unknown, antiviral antibody has been postulated to bring the virus in close proximity to the plasma membrane, thus increasing the likelihood of a receptor interaction. As well, some have argued in favor of a role for Fc receptor interaction induced phagocytosis in antibody dependent enhancement (ADE) of infection. Regardless of the precise mechanism(s), several viral infections appear to be enhanced by the presence of antiviral antibodies including West Nile virus, HIV, and Ebola virus (Buchmeier & Oldstone, 1978; Gubler et al., 2007; Robinson et al., 1988; Takada et al., 2003). Perhaps the most widely examined example of ADE can be found in dengue virus infections.

Dengue virus, a member of the *Flaviviridae* family of viruses with worldwide distribution, is estimated to infect 50 to 100 million people annually (Gubler, 1997). Primary infection is typically asymptomatic, but can result in a minor febrile illness termed dengue fever (DF), however it is estimated that 500,000 people are afflicted with more severe clinical manifestations of dengue viral infection, known as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Capillary leakage, increased vascular permeability, hemorrhage, and thrombocytopenia distinguish DHF from DF. DHF, where plasma leakage is so severe as to induce shock, is referred to as DSS a severe and potentially fatal outcome of dengue infection.

The observation that severe adverse outcomes to dengue virus infection are almost exclusively the result of secondary infection with a heterotypic serotype of DV has lead many to postulate that DV induced tissue damage is immune mediated. Three theories dominate the literature to explain this unique finding (reviewed in Kurane, 2007; Mathew & Rothman, 2008). The first hypothesis proposes that the more severe clinical manifestations of DHF and DSS are due to the presence of preexisting antibodies to a heterologous serotype of dengue virus, which facilitate antibody dependent enhancement of infection (Littau et al., 1990). The second theory, for which there is much support, suggests that both qualitative and quantitative differences in the T-cell response to a heterologous serotype are responsible for the clinical manifestations of DHV. Cross-reactive T cells in the memory compartment from the primary infection are selectively expanded; these T cells have lower avidity for the secondary strain of virus, are unable to control viral replication and lead to altered IFN γ /TNF α (tumor necrosis factor alpha) balance contributing to tissue damage (Beaumier & Rothman, 2009; Mangada & Rothman, 2005). The more recent third hypothesis suggests that DHF/DSS are a consequence of infection with more virulent dengue viral strains, while less virulent strains lead to DF. Mounting evidence for all three hypotheses strongly suggest that multiple factors likely contribute to dengue virus pathogenesis.

Epidemiological data in support of a role for heterotypic antibody in exacerbating disease severity upon secondary infection can be found in multiple settings. First, the presence of nonneutralizing antibody to a heterotypic serotype at the time of secondary infection strongly correlates with DHF progression. Second, infants enduring a primary infection

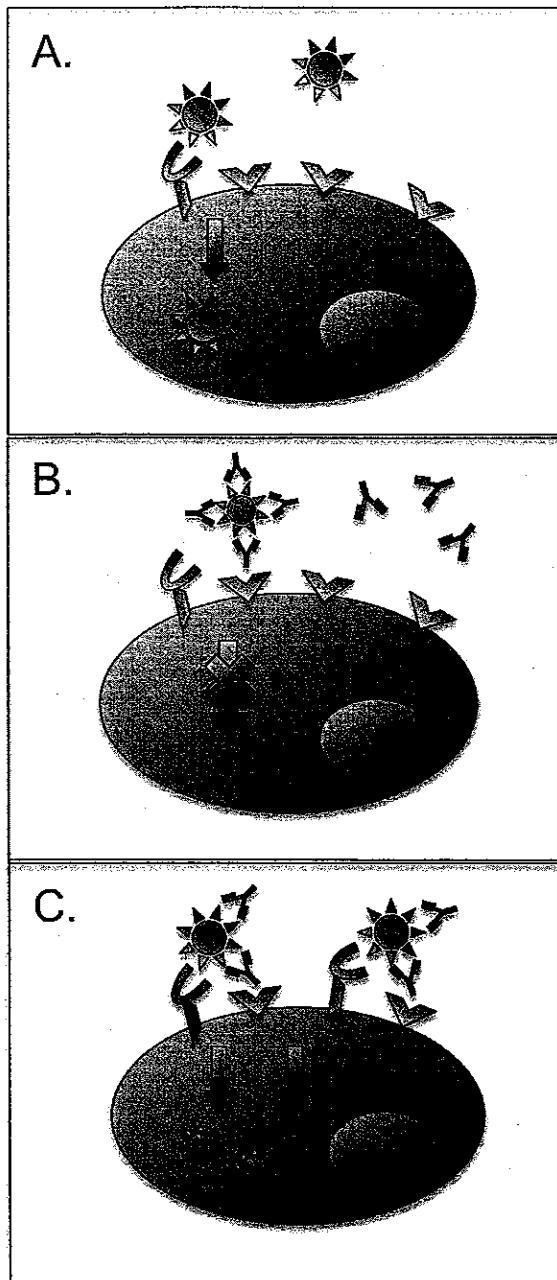


FIGURE 1 Model of antibody-dependent enhancement of viral infection. In the absence of antibody, receptors on the surface of the virion attach to the cell via interactions with the cognate receptor on the surface of the cell, followed by adsorption of the virus into the host cell (A). In the presence of sufficient concentration of neutralizing antibody, viral adsorption or attachment of the virus to the cell is blocked (B). The presence of subneutralizing (either heterotypic or insufficient titer of neutralizing) preexisting antibody may enhance viral attachment or adsorption to the surface of Fc-receptor bearing cells. Alternatively, the simultaneous engagement Fc receptors on the surface of an infected cell may enhance the ability of the virus to replicate in Fc receptor bearing cells downstream of attachment and adsorption or alter the function of the infected APC (C).

with dengue virus who have passively acquired maternal antibody to a heterotypic strain of dengue virus have been documented as developing DHF. Furthermore, *in vitro* data has demonstrated ADE of DV in infected cultures. More convincingly, the recent development of an animal model of DHF supports a role for preexisting antibody in DV pathogenesis (Shrestha et al., 2006; Zellweger et al., 2010). The study revealed that antibody can be sufficient to turn a nonlethal disease into a lethal one. Interestingly, it was found that even neutralizing antibody can enhance pathogenesis if present at subneutralizing concentrations (Fig. 1). While previous studies have centered on *in vitro* models of ADE, the Shrestha model is the first to demonstrate an *in vivo* pathogenic role for antibody in DV pathogenesis.

VIRUS-INDUCED AUTOIMMUNITY

Autoreactive T cells are normally eliminated by clonal deletion in the thymus. However, T cells with minimal affinity for their cognate self-peptide can escape deletion. Additionally, not all self-antigens are available for display during this critical phase of the developing TCR repertoire. Furthermore, the inherent degeneracy of the TCR means that small sequence variation between self and non-self-peptide antigen may lead to the recognition of autoantigen as foreign by an otherwise normal TCR. Activation of T cells generally requires presentation of antigen in the context of an activated APC. Viral infection may provide the needed second stimulus for activation of autoreactive T cells.

The process by which viruses may induce or enhance autoimmunity is hypothesized to occur by a number of mechanisms (reviewed in Filippi & von Herrath, 2008; Olson et al., 2001; von Herrath & Oldstone, 1996). One model of virus-induced autoimmune disease proposes that autoimmunity initiates when previously sequestered tissue antigens become exposed in an inflammatory environment. A second model promotes bystander activation where autoreactive T cells are activated by the cytokine milieu released during a normal adaptive immune response to viral invasion. A third model suggests that autoimmunity may be initiated by the release of sequestered tissue antigens as a result of virus-induced cytotoxicity, thus leading to the activation of autoreactive T cells. A fourth model supports the idea that induction of autoimmunity can be attributed to molecular mimicry, where viral encoded antigen bearing a striking sequence similarity to a host cell peptide, leads to host tissue destruction by an antiviral reactive (not autoreactive) T-cell response.

IMPLICATIONS OF VIRUS INDUCED IMMUNOPATHOLOGY IN ANTIVIRAL VACCINATION STRATEGIES

In light of recent advancements in our understanding of virus-induced pathology, it is clear that each virus poses a different set of challenges; a protective immune response for one virus can prove to be pathological in another. Recent clinical trials for several different vaccines, where vaccinated groups had elevated risk for infection and or disease than their naive cohorts, have highlighted the necessity for continued basic science research into the precise mechanisms of virus-induced immunopathology. One example of this can be found in the vastly different outcomes achieved with different strategies in RSV vaccination. Whereas vaccination of children with live attenuated virus provided protection, 69% of infants from 6 to 23 months in age vaccinated with formalin-inactivated virus suffered from acute febrile pneumonia (requiring hospitalization, as compared to 9% of unvaccinated children the same age) upon subsequent natural infection with RSV

(Kapikian et al., 1969). Mouse models showed that adoptive transfer of CD4 T cells from mice experiencing an immunopathological response could transfer disease; depletion studies further confirmed these results. These findings suggest that CD4 T cells are acting as effectors, and not helpers, in the context of RSV pathology. This is in contrast to recent studies of hantavirus infection of its natural host, the deer mouse, where elevated levels of CD4⁺ regulatory T cells were found (Schountz et al., 2007). Deer mice do not develop an HPS-like response, despite being potent reservoirs for viral replication; this has led to much interest into whether the elevated Treg response observed in the natural host may be mediating protection against pathology by subduing the effector T-cell response. The observation that Tregs may alleviate downstream pathology due to an overly activated immune response opens up a new paradigm in the development of Treg therapeutics to treat virus-induced pathology. Additionally, while the development of antiviral antibody in the vaccinated host has long been a goal of vaccine design, studies in dengue virus pathogenesis, induced by the presence of heterotypic antibody, caution against generalized assumptions on the correlates of protection. Custom vaccine design tailored to the virus in question and the pathology induced should provide protection against either infection or pathology through the induction of the most effective arm of the immune response to a particular pathogen.

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