Review

A systematic approach to virus–virus interactions

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A B S T R A C T

A virus–virus interaction is a measurable difference in the course of infection of one virus as a result of a concurrent or prior infection by a different species or strain of virus. Many such interactions have been discovered by chance, yet they have rarely been studied systematically. Increasing evidence suggests that virus–virus interactions are common and may be critical to understanding viral pathogenesis in natural hosts. In this review we propose a system for classifying virus–virus interactions by organizing them into three main categories: (1) direct interactions of viral genes or gene products, (2) indirect interactions that result from alterations in the host environment, and (3) immunological interactions. We have so far identified 15 subtypes of interaction and assigned each to one of these categories. It is anticipated that this framework will provide for a more systematic approach to investigating virus–virus interactions, both at the cellular and organismal levels.

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By design, viral infections in the laboratory almost always occur in the absence of other viruses. While this may be a logical starting point for virus research, viral infections in nature rarely occur in isolation. Polymerase chain reaction (PCR)-based techniques have revealed that persistent viral infections are present in all domains of life. Archaea can be hosts to several types of phage viruses (Snyder et al., 2003). Most environmental and commensal bacterial isolates are infected with one or more phage viruses

(Ackermann and Kropinski, 2007). Yeasts, including Endomyces magnusii (Pospisek et al., 1994) and even laboratory strains of Saccharomyces cerevisiae harbor multiple types of endogenous RNA viruses (Fujimura and Esteban, 2007). Filamentous fungi are similarly affected (Nogawa et al., 1993). Phytoplankton are commonly infected by dsDNA viruses (Bellec et al., 2010), while both wild and domesticated vascular plants have been shown to carry numerous persistent viral infections, including badnaviruses (Kenyon et al., 2008). Finally, genomic sequencing of animals has shown that chromosomes of both invertebrates and vertebrates are permeated with genetic sequences that resemble integrated retroviruses, in various states of viability (Gifford and Tristem, 2003). Approximately 8% of human genomic DNA, for example, is derived from retroviral genomes (Tristem, 2000). However, persistent infections in animals are not limited to retroviruses. The picorna-like Nora virus has been detected in all *Drosophila melanogaster* strains tested, both laboratory and wild caught (Habayeb et al., 2006), and life-long herpesvirus infections are well known in humans (Chen and Hudnall, 2006; Pancharoen et al., 2001) as well as marine bivalves, fish, reptiles, birds, and other mammals from mice to elephants (VanDevanter et al., 1996). Therefore in any individual, persistent, sometimes congenital, often asymptomatic viral infections provide a background onto which all future viral infections are superimposed.

Given the now significant evidence for ubiquitous endogenous viral infections in all domains of living things, virus coinfections would seem to be the rule rather than the exception in nature, if not the laboratory. Yet, they have rarely been systematically studied for possible effects of one virus on the other, with most documented interactions having been discovered accidently. It is certainly true that coinfection may not result in interactions for all virus species. However, because many viruses induce profound changes in their host, it seems likely that virus–virus interactions are common and may be critical to understanding viral pathogenesis and evolution. Therefore, in this review we identify known and potential types of virus–virus interactions (VVIs) and organize them into three categories: (1) direct interactions of viral genes or gene products, (2) indirect interactions that result from alterations in the host environment, and (3) a subset of indirect interactions called immunological interactions, unique to organisms equipped with an adaptive immune system. We have so far identified fifteen subtypes of VVI and assigned each to one of the three major categories (Table 1). This framework provides a systematic approach to investigating VVI, both at the cellular and organismal levels.

As a first step, it is necessary to define VVI. We define a VVI as a measurable difference in the course of infection of one virus as a result of a concurrent or prior infection by a different species or strain of virus. A concurrent infection may include infection of the same cell by two or more virus species, or two viruses may infect different cell types within one organism and produce measurable VVI. Measurable differences include changes in tissue permissiveness or tropism, viral replication, patterns of progeny production and release, latency, pathology including immunopathology, and immunological responses.

Of course the simple case of a prior viral infection conferring protective immunity against future infections with an immunologically identical virus is well known. But this interaction follows directly from the role of the adaptive immune system, and is therefore a rather uninteresting sort of interaction. A trivial case also exists with virus-induced generalized immunosuppression, as seen with human immunodeficiency virus (HIV)/AIDS. Generalized immunosuppression, regardless of the cause, results in increased replication and pathology by some viruses that have a benign disease course in immunocompetent persons. However, this effect is not specific to viral pathogens. Therefore, the discussion of VVI involving virus-induced immunosuppression will be limited here to those in which there is evidence of other viruses impacting the course of infection of the immunosuppressive virus, or evidence of direct interaction of proteins or nucleic acids of the immunosuppressive virus with proteins or nucleic acids of a coinfecting virus (Lisco et al., 2009). These uninformative examples aside, we have collected reports of VVI involving unexpected direct, environmental, and immunological interactions and used them to create what is intended to be a growing online database of these important phenomena. In the sections below, the current subtypes of VVI are each described and illustrated with a few examples. Some categories have many more currently known examples than those described here, which are included in the online database. We do not mean to represent either the examples below nor the online list as a complete collection. Instead, our aim is to provide the framework to launch a publicly available collection of VVI which allows continuous updates by and for the scientific community.

1. Direct interactions of viral gene products

We define a direct VVI as an occurrence in which nucleic acids or proteins of one virus physically interact with the genes or gene products of a coinfecting virus. This definition encompasses six different subtypes of interaction: helper viruses, pseudotype viruses, superinfection exclusion, genomic recombination, embedded viruses, and heterologous transactivation. Direct interactions require coinfection of the same cell to take place, but the infections need not take place close in time. In several cases of documented direct interactions described below, cells latently infected with one virus may be infected by the second virus years, or even millenia later if the initial viral genome is incorporated into the germline of the host.

1.1. Helper-dependent viruses

A helper-dependent virus is any virus that is replication defective on its own, and therefore requires the gene products of another virus to produce infectious progeny. Engineered recombinant helper virus/helper-dependent virus pairs have been developed as safe viral vector technologies (Dorigo et al., 2004; Marconi et al., 2008), but several natural pairs of such viruses are also documented. One of the first helper-dependent viruses described was bacteriophage P4, a bacteria-infecting virus that is able to replicate its own genome, but requires the presence of a coinfecting bacteriophage, such as P2, to provide capsid components and cell lysis (Shore et al., 1978; Six and Klug, 1973). In plants, the carrot mottle virus of the Umbravirus genus has been shown to be dependent upon viruses of the Luteoviridae family for encapsidation and

Table 1
Categories of virus–virus interaction.

I. Direct interactions
a. Helper-dependent viruses
b. Pseudotype viruses
c. Superinfection exclusion
d. Genomic recombination
e. Embedded viruses
f. Heterologous transactivation
II. Environmental interactions
a. Indirect transactivation of genes
b. Breakdown of physical barriers
c. Altered receptor expression
d. Heterologous activation of pro-drugs
e. Modification of the interferon-induced antiviral state
III. Immune effects
a. Altered immune cell activation
b. Induction of autoimmunity
c. Antibody-dependent enhancement of infection
d. Heterologous immunity

transmission by aphids (Waterhouse and Murant, 2008). A mammalian helper-dependent virus is adeno-associated virus (AAV), a replication-defective parvovirus that generally requires a host cell that is coinfected with an adenovirus or herpesvirus in order for virions to be produced and escape the host cell (Buller et al., 1981; Goncalves, 2005). Since the original description of AAV, it has been discovered that genotoxic stress and other factors may also make a host cell permissive for AAV progeny production, indicating that AAV is not entirely replication defective (Meyers et al., 2000; Yalkinoglu et al., 1988). A more clearly defined case is that of hepatitis D virus (HDV), a human pathogen. Originally, discovered in the 1970s as a subtype of hepatitis B virus (HBV), further studies led to the understanding that HDV only occurred in HBV infected individuals. Although the small viroid-like HDV is able to reproduce its own RNA and ribonucleoprotein capsids, it requires the HBV membrane glycoprotein, hepatitis B surface antigen (HbsAg) in order to associate with cell membranes and bud as infectious particles (Rizzetto, 2009). Therefore, naturally occurring helper-dependent viruses appear to be dominated by non-enveloped viruses that can replicate their genome autonomously and only require a helper virus for packaging and/or release.

It should be noted that the interaction between a helper-dependent virus and its respective helper virus is not necessarily unidirectional. Both AAV and P4 significantly inhibit the replication of their helper viruses (Barrett et al., 1973; Timpe et al., 2006). In contrast, HDV coinfection with HBV results in increased activity of both viruses, often resulting in a more severe clinical course than HBV alone (Rizzetto, 2009).

1.2. Pseudotyped viruses

Virus pseudotyping occurs when two species of virus coinfect a host cell and progeny virions are produced that contain nucleic acid of one parental virus and some structural proteins of the other parental virus. This phenomenon, also called phenotypic mixing, may involve capsid proteins, or in the case of enveloped viruses, only membrane glycoproteins (Zavada, 1976). Various bacteriophage, plant viruses, and animal viruses have all been observed to produce phenotypically mixed progeny from coinfections (Zavada, 1976). Some coinfections result in pseudotyped virions from both parental genomes, while other interactions result in pseudotyped virions of only one type (Certo et al., 1998). For example coinfection of human syncytiotrophoblasts with human cytomegalovirus and human T-cell leukemia-lymphoma virus (HTLV-I) results in HTLV-1 capsids within CMV envelopes, but not the reverse (Toth et al., 1995). Pseudotyped viruses are distinct from helper-dependent virus interactions since neither virus requires components of the other to complete its replication cycle.

Envelope glycoproteins are the main receptor binding proteins of most enveloped viruses, and therefore pseudotyped virions often have an expanded host range, able to infect the targets of both parental viruses. Two herpesviruses have been shown to produce pseudotyped human immunodeficiency virus (HIV) or HTLV-1 virions when coinfected with these retroviruses (Heng et al., 1994; Toth et al., 1995). In addition to a hybrid virion morphology, these pseudotyped retroviruses possess an expanded host cell range: herpes-pseudotyped HIV is capable of infecting keratinocytes (Heng et al., 1994). This feature of pseudotyped viruses has been used to advantage in the production of recombinant viral vectors, to expand the range of targets they are able to infect (Funke et al., 2009; Li et al., 2009; Wu et al., 2009).

1.3. Superinfection exclusion.

A third type of direct VVI is viral superinfection exclusion, which occurs when a primary viral infection induces resistance to subsequent infections by similar viruses. Superinfection exclusion is known to occur among bacteriophage, retroviruses, hepadnaviruses, arboviruses, and plant viruses (Brindley et al., 2008; Geib et al., 2003; McAllister and Barrett, 1977; Nethe et al., 2005; Saumet and Lecellier, 2006). Mechanisms of exclusion are diverse and have not been determined in all cases, but all mechanisms described so far depend on direct interaction of products of the primary infection with the secondary infecting virus. For example, the cytoplasmic accumulation of Borna disease virus (BDV) nucleocapsid components prevents a subsequent infection of a different BDV strain or arbovirus type through interference with the polymerase of the secondary virus, inhibiting early viral multiplication steps (Geib et al., 2003). The sim protein of bacteriophage P1 appears to block injection of nucleic acid by superinfecting phage at the cell membrane (Kliem and Dreiseikelmann, 1989), and the equine infectious anemia virus secretes a soluble protein that masks its cell surface receptor, blocking binding of subsequent viruses (Brindley et al., 2008). In plants, interaction of heterologous viral messenger RNA molecules which contain sequence homology induces destruction of both messages by the RNA silencing mechanism and inhibition of replication (Saumet and Lecellier, 2006). Although most examples of superinfection exclusion deal primarily with different strains of the same virus, and inhibition of superinfection is not absolute, better understanding of this VVI has the potential to impact future antiviral development (Federico et al., 1996).

1.4. Genomic recombination.

Coinfections with two or more strains of the same virus species in the same host cell can result in progeny virions that are genetic recombinants of the parental viruses. This phenomenon is arguably the VVI with the most serious consequences for human health. Influenza virus coinfections, by virtue of the virus's segmented genome, readily produce recombinant progeny (Gardner and Shortridge, 1979; Nelson et al., 2008). Worldwide surveillance networks monitor the appearance of recombinant influenza viruses as the dramatic antigenic shift that results often produces a virus to which few people have immunity, increasing the risk of a pandemic (Nuzzo and Lam, 2006). However, due to the relatively short course of influenza infections, coinfections are relatively uncommon (Nelson et al., 2008). Human immunodeficiency virus (HIV) in contrast, is a life-long infection and both coinfections (secondary infection prior to seroconversion) and superinfections are well documented. HIV genomic recombination has been shown to facilitate immune escape (Streeck et al., 2008), evolution of replication-defective HIV variants (Iwabu et al., 2008), and the spread of drug resistance (Burke, 1997), all of which complicate HIV control. Life-long herpesvirus infections also result in homologous recombination between strains *in vivo*, with similar effects on immune control and drug resistance (Chou, 1989; Haberland et al., 1999; Poole et al., 1999). More recently, recombination between attenuated poliovirus vaccine strains and virulent wild enterovirus strains has led to regeneration of virulent polioviruses and cases of polio-like paralysis in regions targeted for poliovirus eradication (Arita et al., 2005; Rakoto-Andrianarivelo et al., 2008). Although not as carefully monitored as human pathogens, recombination-driven altered virulence of viral pathogens of crop plants has also been reported (Ogawa et al., 2008).

1.5. Embedded viruses

Whereas genomic recombination involves nucleic acid transfer between viruses with significant sequence homology and similar if not identical genomic organization, embedded viruses are retroviruses that have integrated themselves into the genomes of unrelated, large DNA viruses. Presumably, integration is random

but only those integrations that leave the DNA virus capable of productive infection propagate and are detected. Two examples, a moth retroviral element embedded into the genome of Autographa californica nuclear polyhedrosis virus (Friesen and Nissen, 1990), and reticuloendotheliosis virus embedded in the fowlpox genome (Hertig et al., 1997), illustrate that the effects of embedded viruses can be multifaceted. In both cases, the embedded retrovirus gains an alternative transmission and entry pathway to hosts, but in the case of the retrovirus embedded in the baculovirus, retroviral gene expression is also activated (Friesen and Nissen, 1990). And for reasons not yet understood, the fowlpox strains carrying the embedded reticuloendotheliosis virus cause immunosuppression in chickens while reticuloendotheliosis virus-free strains do not (Wang et al., 2006).

1.6. Heterologous transactivation

The final type of direct VVI for which we find documentation, involves transactivation of the genes of one virus species by gene products of a heterologous virus. Many viruses encode powerful promoters and transactivating proteins in order to appropriate the cellular transcription machinery for maximum viral gene expression. Direct binding and transactivation of a heterologous viral promoter is documented in the case of cytomegalovirus transactivating protein IE2-86 which binds to the −120 to 20 region of the HIV-1 long terminal repeat (Yurochko et al., 1999) and in the case of human foamy virus bel1 protein which recognizes and binds to the −158 to −118 region of the HIV-1 long terminal repeat (Lee et al., 1992). Epstein-Barr virus (EBV) and hepatitis C virus (HCV) coinfection results in significantly higher HCV production than HCV infection alone. It is known that the EBV gene product responsible for enhanced HCV replication is the transcriptional activation protein EBNA1 (EBV-encoded nuclear antigen-1) (Sugawara et al., 1999) and it therefore seems likely that EBNA-1 enhances HCV replication by direct transactivation, however, the targeted genes in HCV have not been identified. It is possible, however, that EBNA1 activates HCV genes indirectly, as discussed in more detail below. Post-transcriptional heterologous transactivation also takes place. Herpes simplex virus protein US11 is an RNA binding protein that controls post-transcriptional expression of herpes simplex genes. However, during coinfections it also binds and controls splicing of HTLV-1 and HIV-1 transcripts normally controlled by the retroviral proteins Rex and Rev, respectively (Diaz et al., 1996).

2. Indirect (environmental) interactions

Viral infections can cause many pathogenic changes in the host. Often seen during dual infections is acceleration of disease, because of the compounded nature of the two viral cytopathic effects affecting the host in a negative manner. In this section, indirect VVI resulting from alterations in the host environment created by pre-existing or simultaneous coinfections are explored. Five subtypes of indirect environmental VVI are currently recognized: indirect transactivation of genes, breakdown of host physical barriers against infection, altered receptor expression, heterologous activation of antiviral pro-drugs, and modification of the interferon-induced antiviral state.

2.1. Indirect transactivation of heterologous viral genes

While direct binding and activation of viral transactivating proteins to heterologous viral promoters has been documented, more common are reports of viral infections inducing increased expression or activation of cellular transcription factors, which then act on promoters of coinfecting viruses. For example, hepatitis B virus x-protein transactivates promoters containing kappa-B like enhancer elements, both cellular and viral, but not by binding to the elements itself (Twu et al., 1989). Human herpes virus 6 (HHV-6) infection of Epstein-Barr virus (EBV)-infected cells results in transactivation of the EBV zebra gene, but the transactivation appears to be mediated by cellular transcription factors on the EBV promoter (Flamand and Menezes, 1996). The human endogenous retrovirus K (HERV-K) LTR is transactivated by HSV-1 protein ICP0 via increased binding of cellular transcription factor, AP-1 (Kwun et al., 2002). CMV IE1 protein also transactivates an LTR, the HIV LTR, but does so by inducing increased binding of NF-kappa B to the LTR sequence by an unknown mechanism (Kim et al., 1996). A VVI involving another EBV latency protein, LMP2A, illustrates the potential complexity of indirect virus–virus transactivation interactions. EBV infection, and subsequent LMP2A expression in human cells, results in the activation of a superantigen gene encoded by the long integrated and inactivated human endogenous retrovirus K18 (HERV-K18) with serious clinical consequences (Hsiao et al., 2006). However, LMP2A appears to cause gene expression from the remnants of this ancient viral infection by binding to an enhancer 13 kb downstream and transactivating a cellular gene encoded on the opposite strand. Transcription of the cellular gene most likely displaces repressors on the HERV-K18 promoter sequences, resulting in transcription of its *env* superantigen gene (Hsiao et al., 2009).

In summary, indirect heterologous transactivation is probably the most common VVI, with many interactions yet to be discovered. The diversity of mechanisms they represent and our present incomplete understanding of transcriptional control mechanisms increase the challenge of identifying such interactions. Most have been investigated because a coinfection was observed to exacerbate a viral disease. There are potentially other cases of indirect heterologous transactivation that reduce pathology, but are more difficult to detect.

2.2. Altered host susceptibility due to breakdown of physical barriers

Viral replication and progeny production are often characterized by cytopathic effects. Tissue damage that results can compromise physical barriers within the host, allowing secondary infections to gain access to otherwise protected tissues. This type of VVI has been observed in plants, specifically Zucchini squash (*Cucurbita pepo*). Some Cucumber Mosaic Virus strains infect zucchini squash plants but only cause localized infections. However, in plants coinfected with Cucumber mosaic virus and Zucchini yellow mosaic virus, the long distance movement of the Cucumber mosaic virus is facilitated and systemic infection of both viruses is observed (Choi et al., 2002). This synergistic effect, which may also be mediated by viral movement proteins (Melcher, 2000), is readily observed by the overall deterioration of the plant as well as by molecular analysis (Choi et al., 2002).

Examples of this type of VVI also exist for animal viruses. Humans infected with herpes simplex viruses 1 or 2 (HSV-1 or -2) have a higher susceptibility for acquisition of HIV, and a higher possibility of transmission of HIV to other persons (Celum et al., 2004; Sheffield et al., 2007). Both of these situations are associated with the ability of HSV-2 to cause open skin lesions and to recruit CD4+ T cells to the sites of these lesions (Celum, 2004). The recruitment of these cells makes more potential host cells available for acquisition of HIV in a herpesvirus lesion than are found in a traumatic lesion. In the case of someone already HIV infected, active HSV coinfection increases the probability of HIV transmission because infected CD4+ T cells are recruited to the open HSV lesion, increasing production of infectious virus at the skin surface (Celum, 2004).

Another example of barrier compromise allowing increased viral spread involves cytokine mediated tissue damage. Atencio et

al. showed that newborn Balb/c and NIH Swiss mice coinfected with wild-type polyomavirus (A2 strain) and Moloney murine leukemia retrovirus (M-MuLV) exhibit growth inhibition and kidney inflammation, whereas either virus alone rarely produced these symptoms. Coinfection was found to elevate cytokines IL-6, IFN-γ, IL-1β and IL-10 early after infection (7 days) much more than single infections, and may be responsible for the kidney inflammation and runting (Atencio et al., 1995).

2.3. Altered host susceptibility due to altered receptor expression

The density of viral receptors on a prospective host cell is a significant factor in determining whether infection is successful (Agnello et al., 1999; Li et al., 1999). Human immunodeficiency virus, for example, binds to a complex of CD4 protein and either CCR5 or CXCL4 as its receptor, and it therefore almost exclusively infects human CD4+ T cells. Coinfections have been shown to alter the cell types infected by HIV by altering expression of CD4 or the co-receptors CCR5 or CXCL4. Human herpes virus 6 (HHV6) has multiple effects in this system. It upregulates CD4 expression on T cells that are already CD4+ increasing their susceptibility to the HIV virus, but it also induces expression of CD4 on the surface of CD8+ T cells making them susceptible to HIV infection as well (Lusso et al., 1991). In addition, HHV-6 coinfection boosts the production of the CCR5 ligand, RANTES, which binds to CCR5 and inhibits the complex formation between CCR5 and CD4 needed for HIV to infect cells. Exogenous RANTES alone, can mimic this inhibitory effect of HHV6 on HIV infection, but it is only inhibitory to HIV strains that utilize CCR5 as a co-receptor, not CXCL4-tropic strains (Grivel et al., 2001).

Human herpes virus 7 (HHV7) infection also alters cell surface receptor expression in a manner protective against HIV. HHV7 is a T-lymphotrophic virus which also utilizes CD4 as a receptor, and competes directly with HIV for binding sites on host cells. In a host first infected by either HIV or HHV7, CD4 expression on T cells is down-regulated, slowing the spread of a subsequent infection by the other virus (Lisco et al., 2007; Lusso et al., 1994).

2.4. Heterologous activation of pro-drugs

A fourth indirect mechanism by which VVI alter infection outcomes by affecting the host environment is the activation of pro-drugs with antiviral activity. Many nucleoside analog antiviral drugs, such as acyclovir, gancyclovir, and famcyclovir, specifically target herpesvirus infected cells because they must be phosphorylated by herpesvirus-encoded kinases or phosphorylases before becoming active. Once activated, the drugs can be incorporated into nascent herpesvirus genomes by viral polymerases, where they act as chain terminators, preventing replication. Recently, it was shown that acyclovir can be activated by one virus and act on another (Lisco et al., 2008). HIV, lacking a thymidine kinase is usually unaffected by acyclovir. However, in herpesvirus and HIV dual infected cells, acyclovir decreases the replication of HIV as well as the herpesvirus. Acyclovir is phosphorylated by herpesvirus kinases and then moves to directly inhibit HIV reverse transcriptase, having an unintended but beneficial effect for the host(Lisco et al., 2008).

2.5. Modification of the interferon-induced antiviral state

A fifth category of virus-induced change in the host environment that may affect coinfecting viruses involves the innate immune mechanism induced in vertebrates by type I interferons known as the antiviral state. The antiviral state consists of increased expression of a combination of enzymes, which if activated, shut down cellular translation (Galligan et al., 2006; Staeheli, 1990). The most

critical of these enzymes are PKR and 2′-5′ oligoadenylate synthetase (2′-5′OAS). Protein kinase R (PKR) has multiple roles in a cell, but its role in the antiviral state is to phosphorylate eukaryotic translation initiation factor 2 alpha (eIF2α), inactivating it and shutting down protein synthesis (Garcia et al., 2007). The 2′-5′OAS synthesizes unique oligonucleotides which activate RNAseL, initiating destruction of cellular and viral RNA molecules necessary for translation. Activation of both enzymes is dependent on the presence of molecules associated with infection, particularly dsRNA, and their activation usually results in cell death (Staeheli, 1990). Animals with defective type I interferon signaling pathways, PKR, or 2′-5′OAS are much more susceptible to viral infections, indicating the effectiveness of the antiviral state (Levin and Hahn, 1985). However, most viruses have also evolved antagonists of PKR and or 2′-5′OAS (Hengel et al., 2005; Langland et al., 2006; Levy and Garcia-Sastre, 2001). From this information it would seem logical to speculate that an antiviral state antagonist from one virus could benefit a coinfecting virus, and this has been shown to be the case in several *in vitro* systems. Murine cytomegalovirus (MCMV) has two proteins that are known to inhibit PKR, m142 and m143. When these proteins are present and active the virus can readily replicate in the host. In the absence of these two proteins, the antiviral state is activated and MCMV replication is inhibited (Budt et al., 2009). This antiviral state activation can be overcome by introducing the PKR inhibitors encoded by vaccinia virus (E3L) or herpes simplex virus (ICP gamma 34.5) (Budt et al., 2009). A herpes simplex mutant lacking ICP gamma 34.5, in turn can be rescued in CV-1 cells by coinfection with the polyomavirus SV40, due to the SV40 large T antigen's inhibitory effect on the antiviral state downstream of ICP gamma 34.5 (Randazzo et al., 1997), or by inserting human cytomegalovirus genes for PKR antagonists, TRS1 and IRS1 (Cassady, 2005; Shah et al., 2007). One possible natural example of this type of VVI involves the interaction of hepatitis B and hepatitis D viruses. The hepatitis D genomic RNA molecule inhibits PKR-mediated inhibition of translation in a cell free translation system, suggesting that it may protect its helper virus, HBV, from the antiviral state (Robertson et al., 1996). Although the known examples of this virus–virus interaction are so far only demonstrated in artificial systems, given the multiple *in vitro* examples it seems likely that this type of VVI also occurs in nature.

3. Immunological interactions

As the third main category of VVI, we define a subset of indirect virus–virus interactions that occur only in host species with an adaptive immune system. We set these types of interactions apart, because unlike the other indirect VVI, which are dependent on an overlap of the periods of infection of two viruses, immunological interactions can occur between viral infections that are completely separated in time. This is possible because the adaptive immune system of the host organism is permanently changed by its interaction with a virus, even if that infection is completely eliminated from the host, and is changed in a manner very specific to the species and strain of the infecting virus. At present, four types of immunological VVI have been identified. These include altering the activation state of cellular components of the immune system, and induction of autoimmune responses to self-antigens that cross-react with viral antigens. In addition, the humoral immune response to viral pathogens can unexpectedly give rise to antibody-dependent enhancement (ADE) of subsequent viral infections. And finally, coinfections, as well as sequential infections, also indirectly interact by re-shaping the T cell memory repertoire such that the immune response induced by one infection can impact the outcome of a subsequent viral infection in an interaction termed heterologous immunity (Welsh and Selin, 2002).

3.1. Altered immune cell activation

One means by which a virus may sensitize a host for a subsequent infection is by altering the activation state of potential host cells. HIV infection, for example, is associated with human cytomegalovirus (HCMV) infection in part due to HIV's induction of elevated numbers of activated lymphocytes in certain tissues. Since activated lymphocytes are permissive for HCMV infection, this HIV-induced activated cellular state results in a two- to three-fold enhancement of HCMV replication in these tissues (Biancotto et al., 2008). Another example is seen with lactate dehydrogenase-elevating virus (LDV). LDV stimulates polyclonal B lymphocyte activation, resulting in delayed induction of antibodies needed to control other coinfecting viruses. Consequently, Friend virus (FV) infection, which is normally asymptomatic in mice due to timely production of neutralizing antibodies, will upon coinfection with LDV propagate and cause symptomatic disease (Marques et al., 2008).

The prevalence of viral coinfections may also impact the progression of HIV disease in this manner. Specifically, it is not unusual for HIV positive patients to be coinfected with GB virus C (GBV-C) and the persistence of certain genotypes of this virus has been shown to lead to slower HIV progression. (Schwarze-Zander et al., 2006). This positive effect for the host appears to be mediated by elevated expression of interferon gamma and the immune cell activation that results. Higher viral titers of GB virus C are directly correlated with increased serum interferon gamma, which in turn results in increased numbers of circulating mature dendritic cells that may be controlling the HIV infection (Lalle et al., 2008).

3.2. VVI induced autoimmunity

Sequential viral infections have also been associated with generation of autoimmunity in the host. Some viruses are able to break immunological tolerance to "self" by expressing a self-like epitope, but are unable to generate the numbers of autoreactive T cells necessary to trigger an autoimmune response. However, a second infection can, by expanding the autoreactive T cell compartment, cause autoimmunity (Welsh and Fujinami, 2007). Mice transgenic for a lymphocytic choriomeningitis virus (LCMV) nuclear protein remain healthy when infected with LCMV, but a subsequent infection with either poliovirus or vaccinia virus leads to the development of pancreatic inflammation and autoimmune diabetes (Christen et al., 2004; Evans et al., 1996).

Another example of this type of VVI is associated with enteroviruses such as Poliovirus. Enterovirus infections have been shown to be a risk factor for several autoimmune diseases including insulin-dependent diabetes mellitus (IDDM) (Dahlquist et al., 1995; Grist et al., 1978; Hiltunen et al., 1997; Hyoty et al., 1995). Multiple epidemiological studies in humans have established that children that manifest IDDM have had more exposures to enteroviruses than healthy subjects (Andreoletti et al., 1998; Clements et al., 1995; D'Alessio, 1992). Interestingly, in countries where a live attenuated polio vaccine which is known to confer cross-protection to enteroviruses (Juhela et al., 1998) is used to immunize children, the incidence of IDDM is lower than in countries where a killed vaccine that does not induce cross-protection is used. This suggests an association between cross-reactivity of immune responses to different viruses and the development of autoimmune diseases (Juhela et al., 1999).

3.3. Antibody-dependent enhancement of infection

In order to infect animal cells, virus particles usually must bind directly to a specific cell surface molecule in a virus-specific manner (Flint et al., 2004). However, several families of virus are known to take advantage of indirectly binding to the cell surface via cross-linking with antiviral antibodies or virus activated complement components which then bind to host cells bearing Fc or complement receptors (Takada and Kawaoka, 2003). This process in which increased viral replication is produced by exposure to immune sera, is known as antibody-dependent enhancement (ADE) of viral infection. It has been observed in vitro for flaviviruses, coronaviruses and retroviruses (Cummings et al., 2005). Mechanisms underlying ADE are not fully understood, but seem to include increased efficiency of virus binding to host cells, resulting in higher numbers of infected cells. The most well studied case of ADE in humans is dengue hemorrhagic fever (DHF). Interestingly, the severe form of dengue illness, which is often fatal, is strongly associated with pre-existing heterotypic immunity (Burke et al., 1988; Kliks et al., 1988; Sangkawibha et al., 1984). The presence of non-neutralizing antibodies from a previous dengue infection augment viral growth in vitro (Kliks et al., 1989) and in vivo (Halstead, 1979). Also, individuals suffering from a secondary dengue virus infection have higher viremia than those with primary infections (Vaughn et al., 2000), and the presence of anti-dengue antibodies in mothers has been associated with the occurrence of dengue hemorrhagic fever in newborns (Kliks et al., 1988). The phenomenon of ADE is not unique to dengue virus infections. It has been demonstrated to play a role in West Nile virus infections in vitro (Peiris and Porterfield, 1979) and yellow fever virus in vivo (Barrett and Gould, 1986). Moreover, infections by two other members of the Flavivirus family, the yellow fever virus and the Japanese encephalitis virus, have also been shown to be enhanced by ADE (Gould and Buckley, 1989). This process is also thought to be responsible for the enhanced pathogenicity of viral challenges after vaccination with certain formalin inactivated viral vaccines (Porter et al., 1972), including ones for measles (Iankov et al., 2006), respiratory syncytial virus (Ponnuraj et al., 2003), and rabies (Prabhakar and Nathanson, 1981).

3.4. Heterologous immunity

Heterologous immunity gives rise to virus–virus interactions when the outcome of the adaptive immune response to a new viral infection is determined in part by immune memory acquired by the host from prior viral infections. Development of a primary adaptive immune response to a pathogen results in an immunological memory, which consists of expanded numbers of long-lived, circulating T and B lymphocytes recognizing epitopes of that specific pathogen (Welsh et al., 2004). Due to randomized DNA rearrangement processes during the generation of the unique specificities of adaptive immune cells, even genetically identical twins have unique T cell repertoires in their naïve state and therefore show some differences in their responsiveness to the same pathogen. Notably, these variations seem to have limited significance for the effectiveness of the immune response to a new infection (Welsh et al., 2006). However, if even a small subset of a T cell memory pool is cross-reactive with antigens of a later encountered pathogen, it will outcompete newly activated T cell clones and dominate that response. That the degree of heterogeneity in the immunological responses between genetically identical hosts could be dramatically influenced in different directions by the history of infections with seemingly unrelated viruses was long unappreciated (Welsh and Fujinami, 2007; Welsh et al., 2006). However, studies in syngeneic mice have confirmed that the unique identity of memory T cells, raised towards one virus but later activated during an infection with an unrelated heterologous virus, dramatically influence the outcome of the second infection (Selin et al., 1996). This heterologous immunity can result in both beneficial and harmful effects (Chen et al., 2001). In mice, for example, immunity to influenza virus protects the host against vaccinia virus challenge, but enhances the virulence of subsequent cytomegalovirus infections (Chen et al., 2003). While

difficult to study in outbred populations, syngeneic animal models allow investigation of immunological memory after heterologous infections. When the diverse viruses LCMV, poliovirus, vaccinia virus, murine cytomegalovirus, and vesicular stomatitis virus were sequentially introduced into syngeneic hosts, the immunological memory against one infection was dramatically altered after each successive infection (Selin et al., 1996). Thus, the course of each infection is influenced by the T cell memory pool, and with each infection, the T cell memory to previous encountered agents is modified (Welsh and Selin, 2002). The effect of heterologous immunity is seen between many different viruses and disease outcome is dependent on both the nature and the specific order in which the sequentially encountered pathogens were encountered (Chen et al., 2003).

4. Conclusion

Although relatively unexplored as a field of study, VVI have already been documented to have significant and unexpected effects on viral disease severity, host range, transmissability, immunopathology, and vaccine effectiveness. Increased awareness of the potential for virus–virus interactions and a framework for categorizing different types of interactions as described here, would seem to be necessary steps for achieving better understanding of infectious viral diseases in nature. It has long been noted that many viral infections result in mild disease for most infected individuals, moderate disease for some, and fatal disease for a few. The epidemiology of poliomyelitis, influenza, and the recent West Nile Virus outbreak in the United States are prime examples of this phenomenon. When occurring in otherwise healthy individuals, these differences in susceptibility have largely been assumed to be governed by cryptic immunological defects, either inherited or acquired (Kacprzak-Bergman and Nowakowska, 2005; Trammell and Toth, 2008). While this is likely true in some cases, it is also plausible that some variations in susceptibility are determined by virus–virus interactions. Evidence for this is strong in the intensively studied case of HIV/AIDS (Lisco et al., 2009). Investigation of similar interactions for acute viral infections will be challenging, but may allow better identification and protection of the most vulnerable populations during disease outbreaks.

It was not possible, of course, to mention every known virus–virus interaction in this article. Rather, the goal was to provide a framework into which all VVI can be organized. An online database has been established (www.musc.edu/vvi/) with the aim of compiling a referenced, searchable, comprehensive list of VVI, actively updated by contributions from the scientific community via moderated forum. We anticipate that the number of VVI subtypes may expand, as during the course of this investigation hints of interactions that seem plausible but are not yet documented were found; for example, stabilization of viral RNAs by heterologous viral RNA binding proteins. In addition, several cases of VVI described above were discovered simultaneously with a new virus, whose existence was not previously suspected. As a wobble in a star's rotation can indicate the presence of an unseen planet, so the perturbation of a viral replication cycle may indicate the presence of an unknown infection, and a virus–virus interaction.

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