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Genetic and Non-Genetic Interaction between Coinfected Viruses

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Abstract:

Viruses have proven to be of major importance as infectious agents and as models for molecular studies. The viruses provide simple model systems that can be used to address many complex biological problems. The study of virus-virus interactions within host cells has contributed greatly to our understanding of gene function and has provided much knowledge concerning both theorganization and the expression of genetic information.When a single cell infected by multiple viruses, hybrid progeny can be produced that contain mixtures of genetic information of co-infecting parents. Besides this verity of interactions, both genetic and nongenetic, mayoccur between two viruses during coinfection. The coinfected hybrid progeny may occur due to genotypic mixing,phenotypic mixing,enhancement,interference and/or complementation.

In this reviewI represent different type of direct and indirect interactions among different plant viruses, animal viruses and bacterial viruses when they coinfect their respective host cell. In direct interaction nucleic acids or proteins of one virus physically interact with the genes or gene products of a coinfecting virus and this is mediated by complementation to helper dependent virus, phenotypic mixing of coinfected virus, superinfection exclusion, genomic recombination and/or heterologous transactivation. On the other hand, during indirect viral-viral-interaction alterations in progeny virus resulting from the host environment created by pre-existing or simultaneous coinfections are explored and this is mainly responsible for alteration of host susceptibility due to breakdown of physical barriers and/or due to altered receptor expression.

Index Terms: Coinfection, Helper-virus, Phenotypic-mixing, Superinfection-inclusion, Complementation

I. INTRODUCTION

Viruses have proven to be of major importance in medical science both as infectious agents and as models for molecular studies. DNA viruses of animals are used as simple model to address a lot of biological complex problems. With the increasingof human populations and its global mobility, individuals are being exposed to an increasing diversity of viruses. Many approaches are used to study viral coinfections at different organizational levels, ranging from very detailed molecular studies of specific viruses to epidemiological studies at the population level, but very few systems present for the study of multi-level dynamics when a single cell coinfected with more then one virus belong to same group and different.

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Coinfection, where multiple viruses infect a cell simultaneously, is important in the life cycle of some viruses. During coinfection, haploid viral genomes act in a manner similar to those of diploid organisms, exchanging genetic material randomly or preferentially. Reassortment of genome segments may create severely deleterious mutational combinations, thus speeding up the elimination of mutational load. Coinfection may, however, result in complementation, where viruses carrying different deleterious mutations may benefit from the normal products that each can produce, so that both types of viruses can be represented in the offspring. In contrast to recombination, complementation weakens the selection against deleterious mutations. In this way, it contributes to the stability of the whole virus population as it maintains a high level of diversity without sacrificing the overall fitness of the population.

Virus coinfections may lead to cumulative immunosuppression to the host due to synergistic enhancement of pathogenesis and expression of gene and molecule associated with intense disease. The basis of these pathophysiological may be due to direct virus-virus interactions, effect of cohabitating viruses on host cell function, or impaired host immune responses.

The virus-virus interactions (VVI) are measurable difference in the course of infection of one virus if the host cell remain prior infected with different species/strain of virus or concurrent infection by the same. The study of DNA virus-virus interactions within host cells has provided much knowledge concerning both the organization and the expression of genetic information. Measurable differences include changes in tissue permissiveness or tropism, viral replication, patterns of progeny production and release, latency, pathology including immunopathology, and immunological responses. A variety of interactions, both genetic and nongenetic, may occur between two viruses in culture (Fig. 1) directed by direct gene products of the viruses or by indirectly/environmentally. The study of these different types of interactions along their subtypes has contributed greatly to our understanding of viral gene functions.

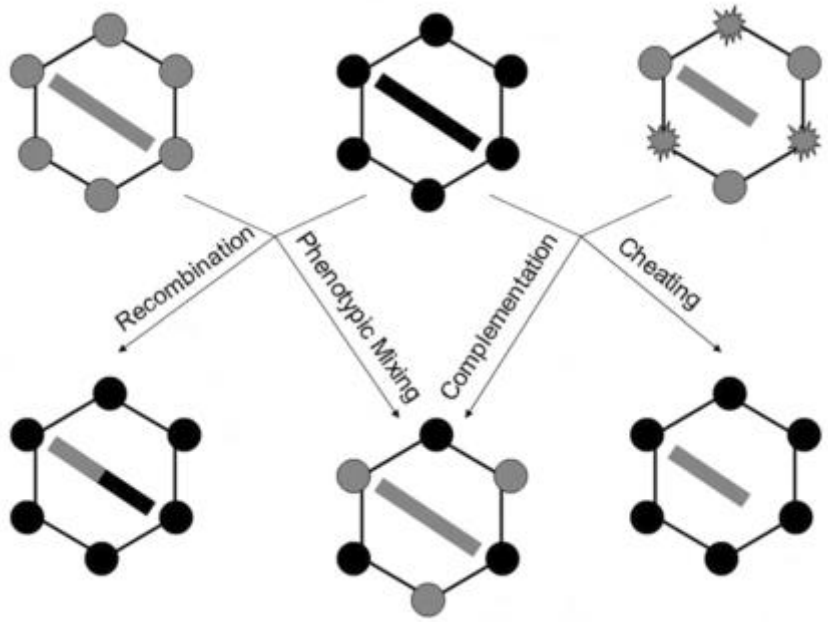

Figure1: Proximate mechanisms occurring as a result of virus interactions within the same cell. The depicted viral particles differ by genotype (black versus gray bars), capsid proteins (black versus gray circles; spiked circles are defective capsid proteins), and genome size (ordinary versus

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shortened, where the shortened genomes are defective due to deletions). Recombination creates hybrid genotypes bearing a portion of genetic information from two or more of the coinfecting parent viruses. Phenotypic mixing can lead to the incorporation of one parent's genome into a capsid containing proteins from multiple parents. Complementation allows one virus that is relatively deficient for a protein or other product to use that which a coinfecting genotype has provided in the intracellular resource pool. Cheating allows an expectedly low fitness genotype, such as a defective deletion mutant, to gain a replication advantage during coinfection.

II. DIRECT INTERACTIONS OF VIRAL GENE PRODUCTS

Direct interaction of viral gene products takes place when a virus infects same cell which was already infected. In this types of interaction nucleic acids or proteins of one virus physically interact with the genes or gene products of a coinfecting virus.

II.A. COMPLEMENTATION TO HELPER DEPENDENT VIRUS

All viruses unable to reproduce in a host cell by themselves. Since viruses are too small, the size of their genome and the coding frame is limited. The lack of coding frame and desired protein causes some viruses to take help of other virus for reproduction. Such viruses are called multiplication defective virus or a helper dependent virus sometimes also called thesatellite virus. Since the genome of these viruses does not include genes encoding the enzymes and/or structural proteins required to replicate and/or reproduce (table 1). As it cannot be replicate without assistance of helper virus they are utilized as synthetic viral vector form transfection of a gene in eukaryotic cell also used as safe technique for gene therapy.

In phage system

Bacteriophage P4, a bacteria-infecting virus is one of the first helper-dependent viruses that is able to replicate its own genome but unable to produce virus structure and lysis of host cell. This virus 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). Another notable example of these types of phage virus interaction is the interaction between the bacteriophages G4 and PhiX174 are both of which aremicroviruses. Both are normally capable of independent replication, but amber mutants in six genes (A, B, E, F, G and H) can replicate if coinfected with the same species of virus with a mutation in a different gene. However,Borrias, et al. (1979) show that only PhiX174 mutants defective for genes E, F, G, and H could be helped by the equivalent gene products of bacteriophage G4, and only bacteriophage G4 H mutants could be helped by the equivalent gene product of PhiX174.

In plant system

In plant, the Carrot mottle virus (CMoV) is a positive-stranded ssRNA virus in the genus Umbravirus has been shown to be dependent upon poleroviruses of the Luteoviridae family for encapsidation and transmission by aphids. In coinfected plant cellsby morphology and sedimentation properties, only one species of viral particle is distinguishable, however, both viral genomes are transmitted to naive plants by the aphid *C. aegopodii* (Waterhouse and Murant, 2008). The tobacco necrosis virus

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(Family Tombuviridae genus necrovirus) is also another example of plant virus that allows the replication of the several satellite tobacco necrosis viruses (STNV).

In animal system

A mammalian helper-dependent virus is adeno-associated virus (AAV), originally identified as a contaminant of adenovirus stocks, is a defective parvovirus that exhibits absolute dependence on coinfection with a helper virus for productive replication. In the absence of a helper virus, AAV efficiently integrates into host cell chromosomes via its inverted terminal repeats but have lake of ability to phenotypic alteration in host cell. Three distinct groups of DNA viruses, adenoviruses, herpesviruses, and poxviruses, complement replication of defective parvoviruses.

The interaction occurs between the "helper" adenovirus and the "defective" AAV by two way. Adenovirus supplies the needed helper function forAAV replication and possibly fortranscription and translation, whereas AAV inhibits lytic replication as well as theoncogenicity of adenovirus. If AAV infection is delayed until 6 or 7 h after adenovirus infection, no inhibition is observed, suggesting a competition between AAV and adenovirus for one or more adenovirus early gene products or for a limited cellular product. Adenovirus helper functions required to support replication of AAV include the E1A, E1B, E2A, E4, and VA-1 RNA genes. Of these essential adenovirus genes, only E1B and E4 appear to directly affect replication of AAV. After coinfection, AAV has a demonstrated capacity to inhibit not only adenovirus DNA replication in a multiplicity-dependent fashion but also the adenovirus oncogenicity. Only the terminal sequences of the AAV genome are essential to restrict adenovirus oncogenicity, which appears to be associated with a decrease in detectable adenovirus tumor antigen by 80%.

In addition to adenoviruses, herpesviruses are known to provide helper activity for AAV multiplication. Both HSV types 1 and 2 (HSV-1 and HSV-2) induce complete and relatively efficient multiplication of AAV in several human cell lines, including KB, HeLa, Hep-2 etc.

In addition to adenoviruses and herpesviruses, a third virus group, the poxviruses, has recently been demonstrated to function as helper viruses for replication of defective parvoviruses.

The coinfection of hepatitis B virus is required for Hepatitis D virus as it contain defective RNA genome that unable produce virion in absence of needed proteins. About 350 millionof people get infected by Hepatitis B virus and among then 5% peoples are superinfected by delta variant of Hepatitis. The coinfection of both virus increases the motility and morbidity rate of hepatitis many times. The delta variant able to multiply and shows pathogenicity in presence of HBV encoded glycoprotein and these types of protein also used by HDV to mature their capsid and surface antigens representation (Rizzetto, 2009).

It should be noted that the although helper dependent virus take advantages form coinfection by helper virus but some time helper virus significantly inhibited (as in case of confections between P4 & P2 bacteriophage; Adeno associated virus & Adenovirus; STNV and Tobacco necrosis virus etc.) of significantly activated (as in case of confections between HDV and BHV etc.).

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TABLE 1. Overview: complementation or replication by unrelated viruses		
Defective/inactive virus	**Complementary virus**	**Helper function**
Hepatitis D (HDV)	Hepatitis B (HBV)	Membrane glycoprotein
Adenovirus-SV40 hybrid	Adenovirus	Trascapsidation
AAV	Adenovirus	E1A, E1B, E2A, E4
	HSV1 & 2	Unknown
	HCMV	Unknown
	Vaccinia virus	Unknown
Adenovirus mutant dl312	Pseudorabies virus	ICP-4
	HCMV	IE gene
Latent HSV-1 and 2	HCMV	Early gene
Adenovirus in simian cells	SV40	-COOH terminus SV40 large T antigen
Carrot mottle virus (CMoV)	Luteoviridae	Encapsidation
P4 bacteriophage	P2 bacteriophage	Encapsidation& lysis

II.B. PHENOTYPIC MIXING OF COINFECTED VIRUS (PSEUDOTYPE VIRUS)

Phenotypic mixing is first recognized by Novick and Szilard in 1951 in bacteriophages, the mixing occurs in protein and nucleic acid level, the recombinant progeny virus was produced when one type of progeny contains nucleic acid of first virus and some structural protein of second virus and other type produce by association of nucleic acid of second virus with protein of first virus. This is occurring when two species of virus coinfect a host. This phenotypic mixing occurs in various bacteriophage, plant viruses, and animal viruses also. In some situation coinfection produce pseudotype virus, where the capsid is totally replaced with coinfected virus during progeny maturation. 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). Phenotypic mixing was take place during maturation of virus (Table 2). Phenotypic mixing may occur between genetically related viruses, e.g. different members of the Picornavirus family, or between genetically unrelated viruses, e.g. Rhabdo- and Paramyxo- viruses.

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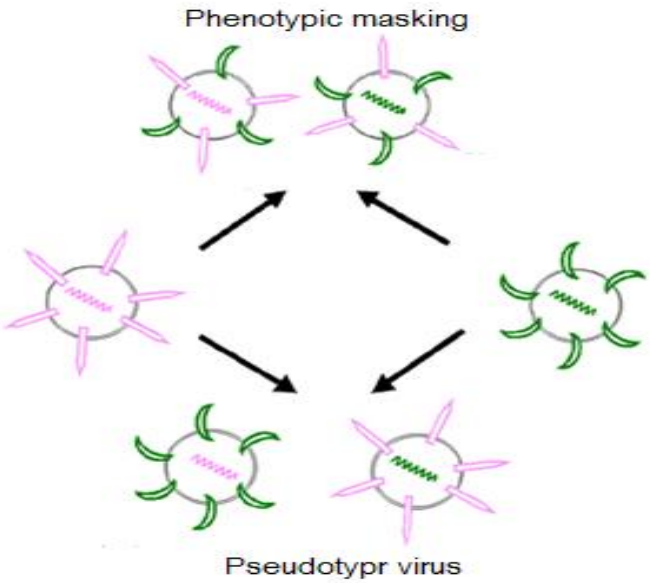

Figure 2: Phenotypic mixing of two related virus upon coinfection.

In phage system

A notable example for coinfection in bacterial system is mixed infections of phages T2 and T4, which have distinct host ranges, at least 15% of T2 genotypes have only the T4 host range (not a combined T2 and T4 host range), and at least 45% of the T4 genotypes have only the T2 host range (Streisinger, 1956). There is additional progeny (at least 16% of T2 genotypes and 12% of T4 genotypes) with a hybrid host range, indicating that the phages have tail fibers from both parental phages (Streisinger, 1956).

In plant system

Tobacco Mosaic Viruses (TMV) are structurally simple viruses consisting of a single positive stranded RNA molecule encapsidated with a helical arrangement of a single type of capsid protein. Each capsid protein subunit interacts with 3 nucleotides of the RNA molecule, with 16.5 capsid subunits per turn of the helix. Many TMV mutants have been identified that have defective capsid proteins. These TMV strains typically produce many copies of their genome and capsid protein but very few intact, infectious progeny particles assemble. The defective capsid proteins are sometimes only defective at higher temperatures, or certain pH levels. Several groups have shown that coinfections with related viruses such as the Nigerian Cowpea Virus, results in encapsidation of the mutant genome by with a capsid consisting of capsid proteins from both viruses.

In animal system

In case of mammalian systemcoinfection of human syncytiotrophoblasts with human T-cell lymphotrophic virus (HTLV-1) and human cytomegalovirus results in asymmetricalpseudotyping of progeny virions: HTLV-1 capsids are packaged in envelopes displaying cytomegalovirus glycoproteins, but the reverses are not detected (Toth et al., 1995).

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TABLE 2. Overview: Example of phenotypic mixing		
Group	**Virus**	**Characteristic**
Adenovirus	Various	Mixed capsids Transcasidation (genomic masking)
Enterovirus	Poliovirus types Poliovirus and Coxsackievirus	Mixed capsids Transcasidation (genomic masking)
	Foot and mouth disease virus and bovine enterovirus	Transcasidation (genomic masking)
Alphavirus	ts mutant of Sindbis virus and other alphavirus	Mixed envelop antigen
Orthomyxovirus	Influenza A and B Influenza and the paramyxovirus, Newcastle disease virus	Mixed envelop antigen Mixed envelop antigen
Paramyxovirus	Strain of Newcastle disease virus SV5 and the rhabdovirus, Vesicular stomatitis virus	Mixed envelop antigen Mixed envelop antigen (or genomic masking)
Leukovirus	Rous Sarcoma virus and avian leucosis virus	Mixed envelop antigen

II.C. PREVENTION OF SECONDARY VIRAL INFECTION (SUPERINFECTION EXCLUSION)

Sometime the pretexting viral infection suppress or prevent infection of second virus to the same cell by same or closely related virus, a phenomenon called superinfection exclusion. These types of phenomena are well documented for various viruses, including important pathogens of animals, plants and humans (Table 3). Although well established mechanism is not available for all the cases but it was found that some proteins of primary infected virus involve to prevent or suppress directly or indirectly to the infectivity of secondary infection of related or same virus.

In phage system

Some bacterial phages encode proteins to achieve superinfection exclusion. These viral proteins can interfere with entry of second virus by modifying host cell receptor for second virus or it prevent nucleic acid release in the host cell.Some bacterial virus degrading bacterial cell wall by releasing peptidoglycanase enzyme to inject nucleic acid, which may be inhibited if the host cell pre-infected with another phage. This type of interaction found in P1 bacteriophage. The sim protein of P1 phage appears to block injection of nucleic acid by superinfecting phage at the cell membrane(Kliem and Dreiseikelmann, 1989).

In plant system

In plants, this type of interaction occurs at RNA level, both genetic and non-geneticRNA, especially messenger RNA of heterologous in nature hybridized to produce double stranded depending homology. This double strand induces RNA splicing mechanism that induce destruction od both RNA and thus prevent vital protein synthesis and viral multiplication (Saumet and Lecellier, 2006).

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In animal system

The Borna Disease Virus (BDV) accumulate its nucleocapsid in cytoplasm of host cell. The components of nucleocapsid of primary infecting virus prevent a subsequent infection of another BVD or related virus such as arbovirus. This is accomplished inhibiting the polymerase enzyme of second virus or interfering with viral multiplication at early stages (Geib et al., 2003).Another example of this type of infection found in anemia virus that prevent subsequent infection by producing some soluble protein that secret outside of host cell and mask the viral receptors and thus blocking the secondary infection(Brindley et al., 2008).

TABLE 3. Many viruses can make superinfection exclusion, few examples are described below:

Family	Virus	Superinfection exclusion protein	strategy
Baculoviridae	AcMNPV	undocumented	undocumented
Closteroviridae	Citrus tristeza virus	p33	undocumented
Flaviridae	Hepatitis C	Undocumented	post entry
Siphoviridae	Enterobacteria phage HK97	gp15	Undocumented
Siphoviridae	Enterobacteria phage T5	Lipoprotein Llp	Blocks T5 entry receptor FhuA
Myoviridae	Enterobacteria phage T4	Immunity protein Imm Protein spackle Sp	Blocks DNA translocation into host cytoplasm Inhibits the lysozyme activity
Siphoviridae	Bacteriophage TP-J34	Lipoprotein LTP	Blocks DNA ejection into host cytoplasm
Siphoviridae	Lactococcus phage Tuc2009	ORF2	Blocks DNA ejection into host cytoplasm
Podoviridae	Enterobacteria phage P22	SieA	Blocks DNA translocation into host cytoplasm
Myoviridae	Enterobacteria phage P1	Sim	Probably blocks DNAtranslocation into host cytoplasm

II.D. COINFECTION INDUCED GENETIC CHANGE (GENOMIC RECOMBINATION)

Viruses are continuously changing as a result of genetic selection. A change in genetic makeup create new serotype of virus, which may be due to minor change though mutation or major change though genetic recombination. The mutation occurs when some error is incorporated in genome due to induced or spontaneous means. The recombination responsible for creation a novel virus by exchange to genetic information between coinfecting viruses. Coinfecting with two of more viruses of same group but different strain to a host cell mixing the genetic makeup and crating recombinant types of viruses with different serotypes of strain. The genetic variability due to recombination mostly occurs in viruses possess RNA genetic materials. This type of recombination mostly found between same group of viruses such as between two influenza viruses of between two herpes

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simplex viruses. The well documented mechanism for virus recombination is independent assortment which occurs during viral genome replication with segmented genome and the other mechanism is incomplete linkage. Both the mechanism produces new serotype of virus and changes its virulence profile (Table 4).

In phage system

The lambda-like phages (lambda and Phi-80) can frequently undergo genomic recombination when coinfecting the same bacterial cell. Ethan Signer (1964) reported that among the progeny of such a coinfection, 0.1 to 1.0% were genetic recombinants with the immunity characteristics of one parent and the host range of the other.

In plant system

The first evidence of genetic recombination in plant RNA viruses was provided by Bujarski & Kaesberg in the Brome mosaic virus (BMV) system. For brome mosaic virus (BMV), a plus-stranded, tripartite-genome virus of monocots, Bujarski & Kaesberg (1986) show that a mutant in the 3' end region of a single BMV RNA genomic component can be repaired during the development of infection by recombination with the homologous region of either of the two-remaining wild-type BMV RNA components. This result clearly shows that plant viruses have available powerful recombinatory mechanisms that previously were thought to exist only in animal hosts, thus they are able to adapt and diversify in a manner comparable to animal viruses. Moreover, their observation suggests an increased versatility of viruses for use as vectors in introducing new genes into plants.

In animal system

Recombination by independent assortment has been reported, for example, for the influenza viruses and other orthomyxoviruses (8 segments of single-stranded RNA) and for the reoviruses (10 segments of double-stranded RNA). This mechanism results in an immediate, major antigenic change and is called antigenic shift. Antigenic shifts in influenza virus antigens can give rise to pandemics (worldwide epidemics) of influenza. However,due to the relatively short course of influenza infections, coinfections are relatively uncommon (Nelson et al., 2008).

Human Immunodeficiency Virus (HIV) is a lifelong 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.

Lifelong 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).

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TABLE 4. Example of Genetic recombination		
Group	**Virus**	**Characteristic**
Poxviridae	Vaccinia and Rabbitpox Rabbitpox	Demonstrated in single cell u mutants recombine ts mutants recombine PK-negative mutants do not recombine
Indovirus	Frog virus 3	Between ts mutants
Herpesvirus	Herpes simplex virus	Between type 1 & 2 Between ts mutants
Adenovirus	Adenovirus 5 Adenovirus and polyomavirus SV40 Adenovirus 12 and cellular DNA	Between ts mutants Some hybris are non-defective In transformed baby hamster kidney cells
Polyomavirus	Polyomavirus SV40 and cellular DNA	Between ts mutants In transformed 3T3 cells
Enterovirus	Poliovirus type I Foot-and-mouth disease virus	Between ts mutants Between ts mutants
Orthomyxovirus	Influenza A Influenza A	Between different strains Between ts mutants
Reovirus	Reovirus 3	Between ts mutants

II.E. VIRAL GENE ACTIVATION BY COINFECTED VIRUS (HETEROLOGOUS TRANSACTIVATION)

Another important aspect viral coinfection is the 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.

In animal system

In infected cells, HIV replication is regulated at least by three virus encoded proteins. The product of tat gene is a positive transcriptional regulator; the product of rev gene regulates the transport of viral mRNA encoding the structural proteins from the nucleus to the cytoplasm while the products of the nef gene may have a negative regulatory effect. However, the transcriptional activity of the promoter (LTR) can also be stimulated by various extracellular stimuli such as mitogens, cytokines and differentiation factors, or by infection with several heterologous viruses including the herpesviruses that often accompany HIV infection in AIDS patients. The molecular mechanism by which the herpesviruses enhance the transcriptional activity of HIV-LTR is not clear. However, it was shown that activation is mediated by the products of herpesvirus immediate early (IE) genes and probably proceeds through stimulation of cellular transcriptional factors such as NF-κB (Pitha&Bednarik).Epstein Bar 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

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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. 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).

III. *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 resultingfrom alterations in the host environment created by pre-existing or simultaneous coinfections are explored. Different subtypes of indirect environmental VVI are currently during viral coinfection.

III.A. 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.

In plant system

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).

In animal system

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 $CD4^+$Tcells are recruited to the open HSV lesion, increasing production of infectious virus at the skin surface(Celum, 2004).

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III.B. 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 up regulates 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).

III.C. HETEROLOGOUS ACTIVATION OF PRO-DRUGS

A third indirect mechanism by which VVI alters infection outcomes by affecting the host environment is the activation of pro-drugs with anti-viral activity. Many nucleoside analog anti-viral 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).

IV. CONCLUSION

Biological systems are organized at many different levels, and this section describes the longer-term, ultimate effects of viral coinfection on these various levels. Recognized levels of biological organization include genome, individual, population, and community. Viral coinfection can influence viral evolution on all these levels. Coinfection holds immediate consequences for the genotypic and phenotypic makeup of the resulting viral progeny, as well as the relative fitness of the coinfecting parent viruses. Different possible consequences are genetic exchange (sex), phenotypic mixing, complementation, and intracellular competition. Determining the relative importance of the proximate mechanisms operating within the cell is one of the biggest challenges in studying the evolutionary ecology of multi-virus infections. The VVI have already been documented to have

significant and unexpected effects on viral disease severity, host range, transmissibility, 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. 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.

REFERENCES

1. Andreoletti, L., Hober, D., Hober-Vandenberghe, C., Fajardy, I., Belaich, S., Lambert, V., Vantyghem, M.C., Lefebvre, J. and Wattre, P. (1998) Coxsackie B virus infection and beta cell autoantibodies in newly diagnosed IDDM adult patients. Clin Diagn Virol 9(2-3), 125-33.
2. Arita, M., Zhu, S.L., Yoshida, H., Yoneyama, T., Miyamura, T. and Shimizu, H. (2005) A Sabin 3-derived poliovirus recombinant contained a sequence homologous with indigenous human enterovirus species C in the viral polymerase coding region. J Virol 79(20), 12650-7.
3. Atencio, I.A., Belli, B., Hobbs, M., Cheng, S.F., Villarreal, L.P. and Fan, H. (1995) A model for mixed virus disease: co-infection with Moloney murine leukemia virus potentiates runting induced by polyomavirus (A2 strain) in Balb/c and NIH Swiss mice. Virology 212(2), 356-66.
4. Barrett, A.D. and Gould, E.A. (1986) Antibody-mediated early death in vivo after infection with yellow fever virus. J Gen Virol 67 (Pt 11), 2539-42.
5. Biancotto, A., Iglehart, S.J., Lisco, A., Vanpouille, C., Grivel, J.C., Lurain, N.S., Reichelderfer, P.S. and Margolis, L.B. (2008) Upregulation of human cytomegalovirus by HIV type 1 in human lymphoid tissue ex vivo. AIDS Res Hum Retroviruses 24(3), 453-62.
6. Brindley, M.A., Zhang, B., Montelaro, R.C. and Maury, W. (2008) An equine infectious anemia virus variant superinfects cells through novel receptor interactions. J Virol 82(19), 9425-32.
7. Cassady, K.A. (2005) Human cytomegalovirus TRS1 and IRS1 gene products block the double-stranded-RNA-activated host protein shutoff response induced by herpes simplex virus type 1 infection. J Virol 79(14), 8707-15.
8. Celum, C., Levine, R., Weaver, M. and Wald, A. (2004) Genital herpes and human immunodeficiency virus: double trouble. Bull World Health Organ 82(6), 447-53.
9. Celum, C.L. (2004) The interaction between herpes simplex virus and human immunodeficiency virus. Herpes 11 Suppl 1, 36A-45A.
10. Cummings, D.A., Schwartz, I.B., Billings, L., Shaw, L.B. and Burke, D.S. (2005) Dynamic effects of antibody-dependent enhancement on the fitness of viruses. Proc Natl Acad Sci U S A 102(42), 15259-64.
11. D'Alessio, D.J. (1992) A case-control study of group B Coxsackievirus immunoglobulin M antibody prevalence and HLA-DR antigens in newly diagnosed cases of insulin- dependent diabetes mellitus. Am J Epidemiol 135(12), 1331-8.
12. Dahlquist, G.G., Ivarsson, S., Lindberg, B. and Forsgren, M. (1995) Maternal enteroviral infection during pregnancy as a risk factor for childhood IDDM. A population-based case-control study. Diabetes 44(4), 408-13.
13. Evans, C.F., Horwitz, M.S., Hobbs, M.V. and Oldstone, M.B. (1996) Viral infection of transgenic mice expressing a viral protein in oligodendrocytes leads to chronic central nervous system autoimmune disease. J Exp Med 184(6), 2371-84.

14. Fujimura, T. and Esteban, R. (2007) Interactions of the RNA polymerase with the viral genome at the 5'- and 3'-ends contribute to 20S RNA narnavirus persistence in yeast. J Biol Chem 282(26), 19011-9.
15. Galligan, C.L., Murooka, T.T., Rahbar, R., Baig, E., Majchrzak-Kita, B. and Fish, E.N. (2006) Interferons and viruses: signaling for supremacy. Immunol Res 35(1-2), 27-40.
16. Gardner, I.D. and Shortridge, K.F. (1979) Recombination as a mechanism in the evolution of influenza viruses: a two-year study of ducks in Hong Kong. Rev Infect Dis 1(5), 885-90.
17. Gifford, R. and Tristem, M. (2003) The evolution, distribution and diversity of endogenous retroviruses. Virus Genes 26(3), 291-315.
18. Hengel, H., Koszinowski, U.H. and Conzelmann, K.K. (2005) Viruses know it all: new insights into IFN networks. Trends Immunol 26(7), 396-401.
19. Hertig, C., Coupar, B.E., Gould, A.R. and Boyle, D.B. (1997) Field and vaccine strains of fowlpox virus carry integrated sequences from the avian retrovirus, reticuloendotheliosis virus. Virology 235(2), 367-76.
20. Iankov, I.D., Pandey, M., Harvey, M., Griesmann, G.E., Federspiel, M.J. and Russell, S.J. (2006) Immunoglobulin g antibody-mediated enhancement of measles virus infection can bypass the protective antiviral immune response. J Virol 80(17), 8530-40.
21. Juhela, S., Hyoty, H., Lonnrot, M., Roivainen, M., Simell, O. and Ilonen, J. (1998) Enterovirus infections and enterovirus specific T-cell responses in infancy. J Med Virol 54(3), 226-32.
22. Kim, S., Yu, S.S. and Kim, V.N. (1996) Essential role of NF-kappa B in transactivation of the human immunodeficiency virus long terminal repeat by the human cytomegalovirus 1E1 protein. J Gen Virol 77 (Pt 1), 83-91.
23. Langland, J.O., Cameron, J.M., Heck, M.C., Jancovich, J.K. and Jacobs, B.L. (2006) Inhibition of PKR by RNA and DNA viruses. Virus Res 119(1), 100-10.
24. Lee, A.H., Lee, K.J., Kim, S. and Sung, Y.C. (1992) Transactivation of human immunodeficiency virus type 1 long terminal repeat-directed gene expression by the human foamy virus bel1 protein requires a specific DNA sequence. J Virol 66(5), 3236-
25. Marques, R., Antunes, I., Eksmond, U., Stoye, J., Hasenkrug, K. and Kassiotis, G. (2008) B lymphocyte activation by coinfection prevents immune control of friend virus infection. J Immunol 181(5), 3432-40.
26. Nogawa, M., Kageyama, T., Nakatani, A., Taguchi, G., Shimosaka, M. and Okazaki, M. (1993)
27. Ponnuraj, E.M., Springer, J., Hayward, A.R., Wilson, H. and Simoes, E.A. (2003) Antibody-dependent enhancement, a possible mechanism in augmented pulmonary disease of respiratory syncytial virus in the Bonnet monkey model. J Infect Dis 187(8), 1257-63.
28. Schoub, B.D., Delpeyroux, F. and Reynes, J.M. (2008) Reemergence of recombinant vaccine-derived poliovirus outbreak in Madagascar. J Infect Dis 197(10), 1427-35.
29. Robertson, H.D., Manche, L. and Mathews, M.B. (1996) Paradoxical interactions between human delta hepatitis agent RNA and the cellular protein kinase PKR. J Virol 70(8), 5611-7.
30. T. Ogawa, P.S., M. Ikegami. (2008) The begomoviruses Honeysuckle yellow vein mosaic virus and Tobacco leaf curl Japan virus with DNAÎ² satellites cause yellow dwarf disease of tomato . Virus Research 137(2), 235-244.
31. Wang, J., Meers, J., Spradbrow, P.B. and Robinson, W.F. (2006) Evaluation of immune effects of fowlpox vaccine strains and field isolates. Vet Microbiol 116(1-3), 106-19.

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32. Wu, Q., Fang, L., Wu, X., Li, B., Luo, R., Yu, Z., Jin, M., Chen, H. and Xiao, S. (2009) A pseudotype baculovirus-mediated vaccine confers protective immunity against lethal challenge with H5N1 avian influenza virus in mice and chickens. Mol Immunol 46(11-12), 2210-7.
33. Yalkinoglu, A.O., Heilbronn, R., Burkle, A., Schlehofer, J.R. and zur Hausen, H. (1988) DNA amplification of adeno-associated virus as a response to cellular genotoxic stress. Cancer Res 48(11), 3123-9.
34. Yurochko, A.D., Huong, S.M. and Huang, E.S. (1999) Identification of human cytomegalovirus target sequences in the human immunodeficiency virus long terminal repeat. Potential role of IE2-86 binding to sequences between -120 and -20 in promoter transactivation. J Hum Virol 2(2), 81-90.
35. Zavada, J. (1976) Viral pseudotypes and phenotypic mixing. Arch Virol 50(1-2), 1-15.