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Viral interference: A review

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Abstract
The inhibition of viral reproduction caused by previous exposure of cells to another virus is popularly known as viral interference or superinfection resistance. The primary virus infecting the cell prevents the replication of secondary virus in that cell, thus making viral interference a very important phenomenon in viral world. It may be simplified by stating that the virus can suppress the shedding of a new virus of the homologous or heterologous type which enters the cell. The mechanisms proposed to explain viral interference may be briefly described as competing by attachment interference where receptors for the superinfecting virus are reduced or blocked, competing for intracellular components required for replication of the host machinery and virus induced interferon interference. The intensity of viral interference however depends on several factors such as adaptation of viruses to host species, pathogenicity of viruses, time of co-infection, and environmental factors. This review highlights the importance of testing of interfering viruses during the molecular screening and viral isolation attempts of infected poultry flocks and other animals so as to identify the consequences of interference during coinfection.

Keywords: viral interference, secondary virus, host, interferon, pathogenicity

Introduction

Viruses are one of the most dangerous living entities, powerful enough to kill more people than a war. Scientists consider them as extremely successful predators dependent on living cells for replication. Viruses have limited pathogenicity in an immunocompetent natural host as they have coevolved with their hosts. Higher vertebrates have developed a complex immune system probably as a result of the constant evolutionary pressure from viral invaders. Viruses exist as extracellular virion particles and intracellular genomes. Virion particles, also known as virions, are susceptible to humoral immune control but more resistant to physical stress than genomes. Virus genomes have well established strategy to evade the host immune response by maintaining limited gene expression. The process of replication and transfer to a new host are not only associated with the production of antigenic proteins in the host that make the virus vulnerable to immune control mechanism but are also essential for a virus species to exist. Viruses have undergone evolution and developed strategies to evade host immune control mechanisms with the help of two classes of viral immunoregulatory proteins. These include proteins that are encoded by genes with sequence homology to cellular genes and also those encoded by genes without this homology. Large DNA viruses such as herpesviruses and poxviruses have shown the presence of viral homologs of host genes involved in the immune system, suggesting that viruses have stolen genes from the host that were modified to benefit of the virus over time. It is believed that viral genes without sequence similarity to cellular genes represent a paradigm for coevolution or simply be examples of proteins for which the host homologs have not yet been identified. Specific motifs required for interaction with the host cellular machinery have been thought to be possessed by these proteins. In addition, viruses have been well known to inhibit the growth and reproduction of other invading viruses new to their cells or "occupied niche". This phenomenon, known as viral interference or superinfection resistance, is the inhibition of viral reproduction caused by previous exposure of cells to another virus. The major factors implicated for viral interference are the generation of interferons by infected cells and the occupation or down-modulation of cellular receptors, however the exact mechanism remains unknown (Laurie *et al.*, 2018) [36].

Kimura *et al.* (1976) [32] described viral interference as a common episode where one cell infected with a virus inhibits the replication of secondary homologous or heterologous viruses.

Dianzani (1975) [9] stated that viruses exert their interfering action either by competing for intracellular replication machinery or through competing for cellular attachment as they reduce or even block the free cell receptors. Thus, in viral interference the pre-infection of a host with one virus affects the multiplication of the second virus. Umar *et al*. (2016) [58] highlighted that veterinary authorities and poultry producers face the problem of mixed infections which are complicated by false diagnosis due to the effect of one virus on another. Shortridge and King (1983) [50] used chicken embryos as a model for studying mixed infection of AIV (Avian Influenza Virus) and NDV (New Castle Disease Virus) and their interference, where clinical and serological parameters were the predominant tools for studying the phenomenon in mixed viral infection for poultry. Since then, many workers have been studying about this aspect (Cherry, 2015; Li *et al*., 2013) [5, 37]. Identification of novel immune-evasion strategies and the analysis of their functions in the context of a viral infection should lead to a better understanding of the immune system and host-virus interaction. This may introduce a breakthrough in treating virus-induced pathology, to design safer and more immunogenic virus vectors as vaccines or gene delivery systems, and to identify new strategies of immune modulation.

Types of Viral Interference

Viral interference, as described above, is a phenomenon whereby infection with one virus (primary) inhibits infection with other viruses (secondary) in the host. This is simply known as superinfection exclusion when the primary virus inhibits the infection of the secondary virus. However, it is quite possible that both the viruses reciprocally inhibit their infections and this is referred to as intrinsic interference (Pesco and Mores, 2009) [47]. Viral interference may be homologous or heterologous in nature. When both viruses belong to the same family, the interference is referred to as homologous viral interference (Singh *et al*., 1997) [51]. A variation of this type of interference, known as heterotypic interference is observed when the viruses involved have different serotypes but belong to the same species (Dittmar *et al*., 1982). Condit (2001) [11, 7] described heterologous viral interference as a negative interaction between viruses from different families. However, in some cases, both the infectious agents can coexist in the same cells and the infection with two different viruses does not result in viral interference. This phenomenon is known as viral accommodation (Sivaram *et al*., 2010). Muturi and Bara (2015) [52, 44] classified mixed infections as coinfections and superinfections based on the time of infection. Coinfections occur when two viruses interact with the host at the same time and superinfections occur when one virus invades the host prior to the second virus. According to Singh *et al.* (1997) [51], the mechanisms involved in viral interference remain elusive, but the inhibition could occur at different levels of the viral replicative cycle, such as binding, entry, replication, and morphogenesis. However, some studies have implicated several other factors, such as defective interfering particles and the RNAi response, in homologous viral interference, and the competition for cellular replication factors and the innate immune response for heterotypic viral interference (Bolling *et al*., 2012) [2].

Mechanism of Viral Interference

The present knowledge on exact mechanism of viral interference is still very fragmentary and it is not known whether various instances of interference described are all based upon related mechanisms, or whether several entirely different reactions are involved. In the light of current information and available literature, various modes of viral interference have been highlighted in this section. These include attachment interference, interferon mediated interference, role of defective interfering particles and other cellular factors.

Attachment interference

The phenomenon of viral interference has been best described as a state induced by an infecting virus that is characterized by the resistance of cells to subsequent infection by a challenge virus (Fenner *et al.*, 1974) [13]. The mechanism involved is believed to be a complex process and many possible modes have been suggested to be responsible. Interference can be due to several different mechanisms, one of which is attachment interference where the interfering virus destroys or blocks the receptors for the superinfecting virus (Fenner *et al.*, 1974) [13].

The role of attachment interference has been well explained in human parainfluenza virus type 3 (HPF3). The envelope of HPF3 consists of two major viral glycoproteins, the hemagglutinin-neuraminidase protein (HN) and the fusion protein (F). Attachment of the virus to the host cell through interaction of HN glycoprotein with a sialic acid-containing cell surface receptor initiates infection of cells by HPF3. This causes penetration and uncoating of the virus from F protein-mediated fusion of the viral envelope with the plasma membrane of the cell, leading to the release of the viral nucleocapsid into the cytoplasm. It has been well documented that in case of HPF3 and other paramyxoviruses, HN as well as F are involved in membrane fusion, and cofunction of the HN and F glycoproteins was found to be necessary for syncytium formation (Horvath *et al.*, 1992; Hu *et al.*, 1992; Lamb, 1993; Moscana and Peluso, 1991) [23, 24, 35, 42]. Infection leads to fusion between cells which involves the interaction of F and HN proteins expressed on the surface of an infected cell with the membrane of an adjacent uninfected cell. HN thus has a receptor destroying potential that plays a significant role in the spread of infection Huberman (*et al.,* 1995) [26]. Many workers have documented the phenomenon of attachment interference as the destruction of viral receptors by the viral neuraminidase for several paramyxoviruses such as Newcastle disease virus NDV (Bratt and Rubin, 1967; 1968) [3, 4] and Sendai virus (Kimura *et al.*, 1976) [32]. The mechanism of attachment interference in NDV was well explained by Baluda (1957) [1] as a result of the destruction of receptors by neuraminidase of the interfering virus. Morrison and McGinnes (1989) [41] also showed that the expression of NDV HN results in resistance to viral infection by NDV. However, whether the resistance mediated by the expressed NDV HN was due to HN's neuraminidase activity remains questionable. Sialoglycoconjugates have been identified as receptors for HPF3 on the basis of their destruction by neuraminidase and this finding has led to the hypothesis that expression of viral neuraminidase on cell surfaces during infection could deplete HPF3 receptors and render cells resistant to infection.

Scientists have initially proposed this mechanism of viral interference for several paramyxoviruses (Baluda, 1957; Bratt and Rubin, 1968) [1, 4].
Soliman *et al.* (2019) [54] showed that the expression of cloned NDV HN resulted in resistance to subsequent infection by NDV; however, the mechanism of this interference mediated by HN remained brane in different amounts. They established a correlation between the level of HN expression, the level of neuraminidase activity, and the level of protection from HPF3 infection. The cell clone WT#1 that exhibited highest levels of HN expression and neuraminidase activity on the cell surface was found to be resistant to infection by HPF3. In contrast, the cell clone WT#2, with lower levels of HN expression and neuraminidase activity, was partially resistant to infection. This partial resistance was evidenced by the slow progression of the cytopathic effect with significantly less virus released into the supernatant fluid after infection compared to control cells and undetectable viral protein in the cell lysates at early time points after infection. They also studied the expression of a neuraminidase-deficient variant HN, C28a HN-GFP, in the cell clone C28a#1.1, which had levels of surface HN expression higher than WT#1 but no detectable neuraminidase activity, and thus correlated neuraminidase activity with protection. The results indicated that C28a#1.1 cells were not protected from infection, despite expressing HN on their surface at levels even higher than the wild-type cell clones. These cells were reported to respond to HPF3 infection identically to the control cells, GFP#1 and 293T, showing the same cytopathic effect and amount of viral replication after infection.
Glycoprotein D (gD) is reported to be one of the essential proteins for penetration into cells for alpha herpes viruses, that further mediates interference with infection (Geraghty *et al.*, 2000; Johnson and Spear, 1989) [16, 28]. Geraghty *et al.* (2000) [16] proposed that cellular expression of the alpha herpes virus gD interferes with the entry of homologous and heterologous virus by blocking access to ligand-binding sites on gD receptors used for entry. In this regard, it was postulated that gD-mediated interference in alpha herpes viruses is important for efficient release of infectious virus by preventing newly enveloped virus from fusing with membranes of the virus-producing cell (Johnson and Spear, 1989). Huberman *et al.* (1995) [28, 26] showed that for HPF3 the neuraminidase activity of HN expressed on the surface allows the virions to be released to begin a new cycle of replication. It has also been reported that the depletion of receptors by the neuraminidase is responsible for the establishment of a persistently infected state (Moscona and Peluso, 1992) [43]. Neuraminidase activity of HN thus depletes the cell of available receptors and has been reported to protect it from reinfection not only by HPF3 but also HPF2. Thus, their findings were in accordance with the hypothesis that presence of neuraminidase activity was required for the establishment of homologous interference for HPF3. HN expression does not suffice to confer resistance to infection without neuraminidase activity. They also postulated that the neuraminidase expressed in the cells during expression of wild-type HN would result in depletion of the HPF3 viral receptors, thus preventing entry. Viral neuraminidase thus acts on the sialic acid receptor during infection, or during expression of wild-type HN. This could thus be an ongoing process in which most of the available receptors would eventually become desialidated and thereby inactivated for viral entry, rendering the cell resistant to infection. Cellular expression of HPF3 HN also depicts a similar mechanism of interference via blockade of HN-binding sites on receptors. Influenza virus also makes use of sialic acid-containing receptors for entry and viral infection has been reported to mediate interference; however, expression of the hemagglutinin (attachment) protein does not protect against viral infection (Morrison and McGinnes, 1989) [41], suggesting that receptor blockade is not important in the interference mechanism for influenza virus. Thus, there are other possible mechanisms that should be focused on.

Interferon mediated interference
Viral infection has been known to stimulate the cell to elaborate protein-like substances of nonviral origin that prevent superinfection with homologous or heterologous viruses. These substances known as interferons are secreted by an infected cell and transmitted to other cells, thereby rendering them resistant to infection. Interferon is a low molecular weight protein produced by the infected cell in response to a stimulus provided by viral nucleic acid(s). It is believed that most cases of viral interference occurring in natural conditions are mediated by interferons, even though other mechanisms are known. The interferon/s produced by an infected cell can migrate to other non infected cells, thus transmitting to them the antiviral-resistant state. Another cellular protein commonly called antiviral protein, is produced under the influence of interferon which is directly responsible for the antiviral state through some alterations of the cellular, virus-directed, proteosynthetic system. The interferon system is not only responsible for antiviral activity but also affects the growth of several nonviral organisms and tumour cells. Controversial effects of interferons have been shown on the immune responses, however the mechanisms underlying these effects are still unclear.
Interferons (IFNs) are well known for their ability to protect cells from viral infection. As described by Kalvakolanu (1999) [29], the basic function of both type I (a and b) and type II (g) IFNs as one of the first anti-viral defense mechanisms is highlighted by the presence of anti-IFN strategies in most viruses. Viral infection not only blocks IFN induced transcriptional responses and the janus kinase (JAK)/signal transducers and activators of transcription (STAT) signal transduction pathways, but also inhibits the activation of IFN effector pathways. It further leads to induction of an anti-viral state in the cell and limits virus replication; which is mainly achieved by inhibiting double-stranded (ds)-RNA-dependent protein kinase (PKR) activation, phosphorylation of eukaryotic translation initiation factor-2a (eIF-2a) and RNase L system, which might degrade viral RNA and arrest translation in the host cell. Poxviruses encode soluble versions of receptors for IFN-a and -b (IFN-a/bR) and IFN-g (IFN-gR), which also block the immune functions of IFNs6. The VVsecreted IFN-a/bR is also localized at the cell surface to protect cells from IFN. Several viruses have been reported to inhibit the activity of IFN-g, a key activator of cellular immunity, by blocking the synthesis or activity of factors required for its production, such as interleukin (IL)-18 or IL-12. In this regard, CPV cytokine response modifier (Crm) A has been shown to inhibit caspase-1, which processes the mature forms of IL-1b and IL-18 (Kotwal, 2000) [34]. Various poxviruses encode soluble IL-18-binding proteins (IL-18BPs); measles virus (MeV) binds CD46 in macrophages and inhibits IL-12 production1 (Kotenko *et al.*, 2000) [33]. Also, herpesviruses and poxviruses express IL-10 homologs

that diminish the Th1 response by downregulating the production of IL-12 (Kotenko *et al*., 2000) [33]. However, activation of the interferon system can be operated *in vitro* and *in vivo* by several non-viral substances such as nucleic acids, polysaccharides, aromatic amines, etc. The use of interferons may play a critical role in the recovery from viral infections and open new perspectives for their possible prophylactic and/or therapeutic use in viral diseases. It can be predicted with confidence that a considerable amount of future research will be directed toward giving the host an added advantage by passive transfer of the antibiotic-like interfering substances, the interferons.

Defective Interfering Particles

One possible factor responsible for homologous viral interference is the presence of Defective Interfering Particles (DIPs). DIPs lack a critical part of the viral genome and are unable to replicate on their own. They are incapable of infection and need a standard virus known as the helper virus or complete virus for co-infection. A partially deleted genome is present in virions which encodes generally normal viral structural proteins with enough genomic information for replication and incorporation into mature virions. However, they cannot perform their own replication without the assistance of a standard helper virus. DIPs have been reported to obtain the viral genome density necessary to specifically interfere with the replication of the parental virus as they have shorter genome capable of preferential replication (Karpf *et al*., 1997) [30].

Inactive viruses have been reported to stop the spread of influenza viruses (Henle and Henle, 1943) [20]. It has been discovered that the interference in viral replication was caused by incomplete forms of the influenza virus and the incomplete forms proliferated only in the presence of the standard viruses (Von Magnus, 1954) [56]. A deleted form of the viral genome is typically called defective interfering (DI) genome (Huang and Baltimore, 1970) [25] and the incomplete forms of viruses were named DIPs. Defective interfering particles have the same structural features as their homologous standard viruses and are reported to be of viral origin. DI genomes are generated by most viruses during viral replication and are simply truncated forms of the viral genomes. They have been found to retain the terminal sequences which are recognized by viral polymerases, the sequences for packaging, a competent initiation site at the 3 end, its complementary sequence at the 5 end, and a structure or sequence required for encapsulation into a nucleocapsid (Mura *et al*., 2017) [45]. Defective interfering particles are not only reported to interfere with the replication of the parental virus but also exhibit cross-interference. Cross-interference has been documented between the closely related VSV-Indiana and VSV-New Jersey viruses (Prevec and Kang, 1970; Schnitzlein and Reichmann, 1976) [48, 49], among different subtypes of the influenza A virus (De and Nayak, 1980) [8] and alpha viruses (Weiss and Schlesinger, 1981) [59]. A typical virus replication cycle is composed of six stages including adsorption, penetration, uncoating, replication, packaging, and release. DIPs or DI genomes have been reported to exert an antiviral effect by suppressing different stages of the virus replication cycle (Yin and Redovich, 2018) [61]. Thus, DIs have been implicated in the establishment and maintenance of persistent viral infections and represent a major self-controlling mechanism for viral replication.

The generation of DIs is a common feature among both RNA and DNA viruses. Participation of viral polymerase is believed to be the most significant factor for the generation of DIs. The viral polymerases, particularly in RNA-dependent viruses, that lack "proofreading" activity are held responsible. It has recently been proposed that *Drosophila melanogaster* cells persistently infected with several nonflavivirus RNA viruses generated cDNAs from the genomes of defective interfering particles through cellular retrotransposon reverse transcriptase-mediated retrotranscription (Goic *et al*., 2013) [19]. Type I IFNs constitute a critical part of innate immunity and are believed to be responsible for the antiviral effects when DIPs/DI genomes are derived. Studies showed evidence linking DIPs to type I IFNs (Frensing *et al*., 2014) [14]. In a study conducted by Dimmock *et al*. (2008) [10], a defective influenza A virus RNA (244RNA) served as a protection for mice against a simultaneous challenge of 10 50% lethal doses of the influenza A/WSN (H1N1) virus. They observed protection from all other subtypes of the influenza A virus and indicated that type I IFNs might play a role in protection due to the presence of strong antigens, defective RNAs and virions. They also suggested the transmission of the preferably packed noninfectious defective virions to nearby cells as a part of the mechanism. Strahle *et al.* (2006) [53] observed similar results for Sendai virus DI genomes where double-stranded RNA was reported to trigger increased expression of type I IFNs.

Researchers have also reported that activation of DIPs/ DI genomes can trigger the maturation of dendritic cells (DCs) *in vivo* and enhance antigen-specific immunity to viruses in the host cells (Mercado-Lopez *et al*., 2013; Frensing *et al*., 2014) [39, 14]. However, the mechanisms are not clearly understood and are worth investigating. Mercado-Lopez *et al.* (2013) [39] have well documented the role of DCs in interference. According to them, the peripheral antigen presenting cells, including DCs, may have a high probability to contact with preferably packed DIPs/DI genomes, which are strongly antigenic but non-infectious. Also, type I IFNs induction leads to increased ability of DCs to bind agonists and process antigen, as well as to up-regulate cytokines, linking innate immunity to adaptive immunity. It is also speculated that production of antibodies exerts antiviral activity and that the expression of type II IFN, also known as IFN-g, following DCs maturation, is involved in inducing specifically antiviral T cells *in vivo* (Mercado-Lopez *et al*., 2013) [39]. The activation of adaptive immune responses that maintain long-lasting protection against reinfection with the same virus essentially require dendritic cells maturation. DIPs of Sendai virus have been reported to provide higher titer of a DC-activating virus replication intermediate product, most probably dsRNA, and it is recognized as pathogen-associated stimuli to trigger the TLR-independent pathway, co-stimulatory molecules, chemokines, chemokine receptors, and numerous pro-inflammatory cytokines (Mellman and Steinman, 2001; Yount *et al*., 2008) [40, 62]. They also reported that DI particles improve the DCs maturation ability and also studied the effect of DI particles when added into a virus that weakly activates DCs. It was found that increased levels of anti-genomic promoter copy-back DIPs and other viral compositions existing in the cell membrane or in endosomal compartments could trigger the DCs maturation genes, thus initiating the type I IFN signaling-dependent and signaling-independent DCs maturation. Thus, the effects of DIPs-induced DC maturation involved in the antiviral mechanisms cannot be ignored and could also be rational in designing viral

vaccines.

Role of Virus nucleic acids and cellular factors in interference

Interference is the mechanism by which a host cell can defend itself against viral infection. The resistance to superinfection not only takes place at the surface of the cell, but it almost certainly does so intracellularly. There is lack of sufficient evidence to implicate genetic or metabolic factors as explanations for competitive antagonism between nucleic acid moieties of two viruses within the same cell. The nucleic acid of the interfering virus may well be essential for initiating the cellular response that leads to interference as the virus contains in its nucleic acid the potential information for its own destruction, mediated by the cellular defenses of the host. There is another possibility that nucleic acids of two interfering viruses might be antagonistic even if they are incapable of genetic interaction. This theory of competitive inhibition of incompatible virus nucleic acids has probably had the greatest vogue and was potentially supported by the important finding that ribonucleic acids (RNA) of plant and animal viruses are infectious even after their protein coats have been stripped off with phenol (Gierer and Schramm, 1956; Colter, 1958) [17, 6]. It has also been found that in order to initiate the process that leads to interference, an influenza virus particle must contain nucleic acid. Gottlieb and Hirst (1956) [18] reported that the RNA-deficient incomplete virus is an inefficient interfering agent which is also genetically defective and cannot participate in cross reactivation. Competitive inhibition is likely to exist if RNA of two viruses should enter the same cell. For example, if the viruses are genetically related but not identical strains of influenza, the yield of each might be reduced and a small proportion of the progeny could emerge as genetic recombinants or mixed phenotypes. It may also be paradoxical that the RNA components of two virus particles can cooperate in the production of recombinant progeny as well as compete with each other. In addition, the capacity of an RNA virus (influenza) to interfere with a DNA virus (vaccinia), cited by Isaacs (1959) [27] as an example of heterologous interference, raises the intriguing question of whether competitive inhibition can occur between nucleic acids with presumed dissimilar metabolic pathways.

In addition to nucleic acids, cellular factors have been assumed to play some role in interference. The important cellular factors like EF1α (highly conserved between different host species as mammals, chicken, and mosquitoes), translation initiation factor eIF5, and ribosomal proteins S6 and L4, participate in several steps of the translation process (Li *et al.*, 2013; Kelen *et al.* 2009) [37, 31], except autoantigen-La, a nuclear protein involved in RNA polymerase III transcription termination (Wolin and Cedervall, 2002) [60] and small RNA biogenesis, which acts as a chaperone and contributes to the retention of nascent RNA in the nucleus or stabilizes the RNA structure. The relocalization of cellular proteins in the cytoplasm has been observed in several RNA viral infections, including flavivirus infections (Meerovitch *et al.*, 1993) [38] and may affect interference.

Factors affecting Viral Interference

Several factors have been known to influence viral interference in the host. These factors include site of viral interference, interfering dose, interfering interval and viral strain/s. However, all these factors are interdependent with a notable effect on each other thus affecting the phenomenon of interference. The first question confronted by virologists interested in the mechanism of the interference phenomenon was whether the primary reaction took place at the cell surface or intracellularly. It is appropriate at this point to examine some of the evidence for interaction between two viruses within a single cell. It has been shown that at least one virus particle per cell is required to induce interference (Baluda, 1957) [1]. However, more than one infectious unit can enter a cell. In such cases, it has been reported that the yield of infectious virus will be diminished if the infecting dose is excessive. According to Von Magnus (1951) [57], the progeny resulting from large inocula of infectious influenza virus is often composed of a preponderance of noninfectious incomplete virus. If the virus is temporarily in the ascendancy, it may stimulate certain cells to produce interferon. If the rate of interferon formation becomes excessive, it might result in a decreased virus titer, thus removing the stimulus for further production of interferon. Consequently, the concentration of interferon, which is not a self-replicating substance, should decline and the virus should increase. In this way it is conceivable that a persistent low grade infection can be established in cell cultures by virtue of cyclic production of both virus and interfering substance in response to viral infection. Also, workers have reported that although there is no assurance that only multiplied infected chick allatoic cells can produce incomplete virus (Fazekas de St. Groth and Graham, 1954) [12], it is almost certainly true that the yield of noninfectious hemagglutinin from HeLa cell cultures depends on the number of virus particles that infect each cell (Henle *et al*., 1955) [21].

Soliman *et al.* (2019) [54] summarized that AIV-NDV (Avian Influenza Virus and Newcastle Disease Virus) viral interference exists with a higher chance for AIV to inhibit NDV replication but the degree of interference may differ in accordance with viral concentrations and strain virulence. Such episodes are of prime importance and should be taken into consideration during field cases diagnosis to avoid false-negative results. Researchers have documented that the more probable AIV-NDV interference mechanism is the competition for cell receptor attachment as both viruses require sialic acid receptors either in the form of sialic acid-containing glycol conjugates for AIV (Murphy *et al*., 1999) or gangliosides and N-glycoproteins for NDV. Another mechanism for viral interference may be due to interferon induction due to primary viral infection that can suppress the replication of the secondary virus (Sonnenfeld and Merigan, 1979; Pantin-Jackwood *et al.*, 2015) [55, 46]. However, this interferon mediated mechanism elucidates the strong inhibition of avNDV even when it was the primary infectious virus, as lentogenic NDV is a weak interferon inducer. Soliman *et al.* (2019) [54] in agreement with the previous studies reported a direct correlation between the degree of interferon induction and the time interval between two infecting viruses (Ge *et al*., 2012; Sonnenfeld and Merigan, 1979) [15, 55] This was taken into consideration in their study, as there was a 12 h lag between the two viral inoculums to allow for maximum interferon activation.

In an attempt to understand the impact of cocirculating human influenza A and B viruses on viral interference, Laurie *et al* (2018) [36] coinfected ferrets with combinations of influenza A and B viruses with intervals of 1–14 days between primary and secondary viral challenge. Viral shedding, as defined by reverse transcription– polymerase chain reaction (RT-PCR)

determined copy number in nasal wash specimens, was monitored by real-time PCR. Interestingly, several patterns of viral shedding after challenge were observed such as prevention of secondary infection, coinfection, shortened secondary infection, delayed secondary infection and no effect as compared to the control group. The first interval of two days (days 1 and 3) represented the start and peak of virus shedding in the upper respiratory tract while day 5 corresponded to decreased viral shedding. Day 7 marked the end of viral shedding while the adaptive immune response was activated during the time period between days 10 and 14. Additionally, these patterns were influenced not only by the interval between primary and secondary viral challenge, but also by the viral strain. Interference was only observed if primary infection occurred up to 7 days before secondary challenge, suggesting that continued shedding of the primary virus may induce a temporary state of immunity that is not seen if secondary infection occurs 10–14 days after primary infection. This pattern was observed with both antigenically related and antigenically unrelated viruses. It was thus concluded that the outcome was dependent on the viral combinations and different influenza viruses induce differing levels of temporary immunity, with the A(H1N1) pdm09 virus being the most effective in the study, followed by influenza B virus and influenza A(H3N2) virus (Laurie *et al.*, 2018) [36].

Conclusion

Viral interference represents the phenomenon where infection of a host cell with one virus frequently prevents or partially inhibits simultaneous propagation of another viral agent in the same host. Also known as sparing effect or cell blockade, viral interference has aroused great interest on account of its theoretical and possibly practical implications. The significant mechanisms proposed towards understanding this phenomenon include direct blockade of viral entry receptors for one virus by another virus, viral competition for host cell resources and viral induction of innate or adaptive immune responses that protect against a related or distinct virus. The literature on this subject has been increasing rapidly in recent years due to prime importance of viral interference in veterinary and related practical aspects. We believe that the study of viral interference may introduce a breakthrough in treating virus-induced pathology by identifying new strategies of immune modulation. The need of the hour is thorough understanding and assessment of the factors affecting viral interference or those causing delay in the replication and infection of viruses so that we can learn better about pathogenicity and transmission of viruses in the host cells. This could provide us with new plans of virus control programs, including new tools for identification and improved protocols of vaccination.

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