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General concepts of virology

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A general review of concepts that relate to virology is provided for the practitioner to refresh and update the information retained since veterinary school. Topics covered include history and classification of viruses, virus pathogenesis, and various host and virus characteristics that influence pathogenesis.

\textbf{History}

With the advent of more sophisticated methods of evaluating virus DNA, it is becoming more apparent that many animals have coevolved with their respective viruses and that new ones have been introduced along the way. There is evidence that thousands of years ago, viruses (e.g., small pox and polio) affected humans; these and other viruses were most likely present long before that [1]. Diseases that were caused by viruses were described long before the actual filterable agents were isolated and called viruses at the end of the nineteenth century. One important step in evaluating viruses was Koch’s postulates. Dr. Koch stated that the following should be demonstrated before determining an agent as being the cause of a disease:

- The agent must be present in every case of the disease.
- The agent must be isolated and grown in vitro.
- The disease must be reproduced when a pure culture is inoculated into a susceptible host.

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The same agent must be recovered again from the experimentally infected host [2].

In 1936, nucleic acid was detected in viruses. In 1940, with the advent of the electron microscope, viruses were visualized for the first time and scientists began to realize their variety in shape and size. By 1949, viruses were being grown in eggs and cell and tissue culture [3].

**Definition of a virus and terminology**

Viruses range in size from a circovirus (14 nm) to a poxvirus (450 nm × 260 nm). Poxviruses are visible under light microscopy. A virion, or mature virus particle, is a simple structure that consists of DNA or RNA which is surrounded by a protein shell (capsid). A subunit of the capsid is called a capsomere; the polypeptide chains of the capsomere are referred to as chemical units. A nucleocapsid consists of nucleic acid and the protein shell together. Some viruses also may have a lipid envelope that is called a peplos; peplomeres are glycoprotein projections that may be present on the peplos [3].

The DNA viruses usually contain double-stranded DNA, whereas the RNA viruses usually contain single-stranded RNA. Examples of double-stranded DNA virus families include Herpesviridae, Poxviridae, Papovaviridae, and Adenoviridae. Single-stranded DNA virus families include Parvoviridae and Circoviridae. Examples of single-stranded RNA virus families include Paramyxoviridae, Rhabdoviridae, Coronaviridae, Togaviridae, Flaviviridae, and Orthomyxoviridae. Double-stranded RNA virus families include Reoviridae and Birnaviridae. Viruses replicate only in living cells and have no energy-yielding apparatus. Unlike bacteria, binary fission does not occur with viruses [4].

**Classification of viruses**

Viruses are classified by morphologic features and chemistry and are distinguished by properties of the genome, virion, and proteins and physical and biologic properties. Different properties that are observed in the genome include nucleic acid type—including distinguishing DNA versus RNA viruses—and genome size and sequence [4]. Different properties that are observed in the virion include capsid symmetry, presence of an envelope, and diameter. Different properties of the proteins include size, function, and amino acid sequence. Differences in physical properties mainly describe the stability of the virus under varied circumstances. Differences in replication strategy may be used to classify viruses by method of transcription, assembly, and release. The most varied differences between viruses is observed in the biological properties (eg, serology, host range, antigenicity, tissue tropism, transmission, vector, epidemiology).
Example of viral classification:
Order = Virales
Family = Viridae (eg, Papovaviridae)
Subfamily = Virinae (eg, Polyomavirinae)
Genus = Virus (eg, Polyomavirus)
Species = a number or animal species name (eg, passerine polyomavirus)

**Virus pathogenesis**

Virus pathogenesis is defined as the mechanism by which a virus replicates in the cell, and in doing so, injures a cell and produces disease. The capacity to produce disease, or the degree of disease, is termed “virulence.” Possible outcomes of virus infection include cell death, persistence, latency, transformation, and nonproductive infection; however, most virus infections are asymptomatic [5].

Disease production commonly results from the virus doing what it needs to do to produce progeny. Virus replication involves several general steps:

The virus must first attach to a cell by way of a surface receptor, followed by entry or penetration into the cell
The virus uncoats within the cell and releases its nucleic acid
For most viruses, the next step is viral transcription to produce mRNA.
    The exception is the single-stranded, positive sense RNA viruses (eg, coronaviruses), whose genome is able to serve as mRNA and undergo immediate translation
For the remaining viruses, translation follows transcription
Replication of the genome is undertaken after initial protein production
After production of viral structural proteins and genome, the components are assembled and viruses are packaged into virions
Lastly, viruses exit the cell. For nonenveloped viruses, this usually occurs through cell lysis, but enveloped viruses may be released through membrane budding and leave the cell intact [6].

During this process, the virus essentially usurps the cellular machinery to carry out these various steps that lead to alteration of cellular function, and in many cases, cell death.
Pathogenesis can be defined at the level of the host. How does the virus enter the host? Where does it replicate? Does it disseminate to other tissues in the host? How is it shed and transmitted? Pathogenesis also can be defined at the level of the virus—What is the virus receptor? How does it enter the cell? How does the infection alter the cell? How is the virus released?

**Host factors that influence pathogenesis**

Many host factors influence pathogenesis, including genetic characteristics of the host and environmental influences. Genetic characteristics of the
host include species, breed, organ, tissue susceptibility, and function at the cellular level (eg, cell receptor types and intracellular hospitality to the virus). Environmental influences of the host include immunity, age, stress, trauma, hormone levels, nutritional status, environmental conditions, and concurrent infection [5].

**Virus factors that influence pathogenesis**

Several virus factors influence pathogenesis, including cytocidal capabilities, cytotoxins, perturbation of cellular function, tissue tropism, and dose and route of inoculation. Some viruses produce proteins that are directly toxic to the cell. These proteins may be structural proteins or replication enzymes, but have lethal effects on the cell. In most cases, however, the death of the cell results from the virus “take over” of the cellular machinery for virus replication. Interference with cellular DNA, RNA, and protein synthesis may occur. The structures of the cell, including cell membrane and cytoskeleton, may be perturbed. Many viruses induce cell lysis for release from the cell, whereas others induce apoptosis. At a minimum, the function of the cell may be altered, and at most, the cell is destroyed. Lastly, cell death or injury may result from the host’s immune response to the virus. This is due to destruction of infected cells and to so-called “bystander killing” of adjacent cells. Significant tissue damage can result in persistent infections where the antigen persists. Lesions may be due to production of immune complexes, cell-mediated destruction, and complement activation [5].

Cellular tropism is an important factor in determining the outcome of infection. It is defined as the specific cells and tissue in the host in which the virus replicates in a natural infection. It is determined by several factors, including the presence of the virus receptor (eg, cluster of differentiation 4 (CD4) expression for feline immunodeficiency virus (FIV) attachment), postpenetration events within the cell (eg, expression of appropriate cellular proteases for influenza), conditional parameters (eg, appropriate pH, temperature), and ability to cross a barrier (eg, blood–brain barrier). For example, viruses whose tissue tropism is the skin (eg, papilloma virus) are less virulent than those that target the central nervous system (eg, encephalitis viruses).

**Course of infection**

Viral infections are either acute or persistent. An acute infection generally has a rapid course with an incubation period of days to weeks and the virus clears the body within 2 to 3 weeks of disease onset. Persistent infections may last months to years and can be characterized as late complications of acute infection or latent, chronic, or slow infections. Persistent infections may be reactivated and cause acute episodes or cause late sequela to infections [5]. They may be associated with immunopathologic disease, may lead to
neoplasia, and are important epidemiologically as a result of recurrence of or continual shedding.

Types of persistent infection include:

Late complications of acute infection—the virus persists, often in the brain (eg, “old dog encephalitis” due to canine distemper virus)

Latent infection—there is intermittent recrudescence of the disease and no virus is shed unless or until the clinical disease recurs (eg, herpesvirus in humans that causes chicken pox in a child and later can cause shingles in an adult)

Chronic infection—the virus is always demonstrable (eg, hepatitis B in humans when a small percentage of affected people become persistently infected and shed the virus continually which can then be associated with cirrhosis or carcinoma)

Slow infection—these viruses have a long incubation period followed by a slow progressive disease (eg, the spongiform encephalopathies such as “mad cow disease”)

Many mechanisms lead to virus persistence (eg, the virus must not be overly cytologic and must avoid detection and elimination by the host immune system). Viruses avoid being overly cytologic by regulating gene expression or by producing less lytic variants. Antigenic variation allows evasion of the host immune system. Other mechanisms that a virus may use to persist include growing in protected sites, persisting in epithelial surfaces, inducing nonneutralizing antibodies or tolerance, or causing defective cell-mediated immunity [5].

Summary

A basic understanding of viruses and how they replicate and produce disease can aid in the management of virus infections. Parameters, such as clinical signs, sample and test selection, prognosis, and control, are implicit in this understanding. Information increases almost daily about known and emerging viruses; this impacts our ability to manage and control infections.

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