SECTION 11 VIRAL DISEASES: GENERAL CONSIDERATIONS

214e Medical Virology

Fred Wang, Elliott Kieff

DEFINING A VIRUS

Viruses are obligate intracellular parasites. They consist of a DNA or RNA genome surrounded by protein. They may also have an outer-membrane lipoprotein envelope. Viruses can replicate only within cells because their nucleic acid does not encode many enzymes necessary for the metabolism of proteins, carbohydrates, or lipids or for the generation of high-energy phosphates. Typically, viral nucleic acids encode messenger RNA (mRNA) and proteins necessary for replicating, packaging, and releasing progeny virus from infected cells.

Viruses differ from virusoids, viroids, and prions. *Virusoids* are nucleic acids that depend on cells and helper viruses for packaging their nucleic acids into virus-like particles. *Viroids* are naked, cyclical, mostly double-strand small RNAs that appear to be restricted to plants, spread from cell to cell, and are replicated by cellular RNA polymerase II. Prions (Chap. 453e) are abnormal proteins that propagate and cause disease by altering the structure of a normal cell protein. Prions cause neurodegenerative diseases such as Creutzfeldt-Jakob disease, Gerstmann-Straüssler disease, kuru, and human or bovine spongiform encephalopathy ("mad cow disease").

VIRUS STRUCTURE

Viral genomes may consist of single- or double-strand DNA, single- or double-strand RNA, single-strand or segmented antisense RNA, or double-strand segmented RNA. Viral nucleic acids may encode only a few genes or more than 100. Sense-strand viral RNA genomes can be translated directly into protein, whereas antisense RNAs must be copied into translatable RNA. Sense and antisense genomes are also referred to as *positive-strand* and *negative-strand genomes*, respectively. Viral nucleic acid is usually associated with virus-encoded nucleoprotein(s) in the virus core. Viral nucleic acids and nucleoproteins are almost always enclosed in a protein *capsid*. Because of the limited genetic complexity of viruses, their capsids are usually composed of multimers of identical *capsomeres* made up of one or a few proteins. Capsids have icosahedral or helical symmetry. Icosahedral capsid structures approximate spheres and have two-, three-, or fivefold axes of symmetry, whereas helical capsid structures have only a twofold axis of symmetry. The nucleic acid, nucleoprotein(s), and protein capsid together are called a *nucleocapsid*.

Many viruses are composed of a nucleic acid core and a capsid. For these viruses, the outer capsid surface mediates contact with uninfected cells' plasma membranes. Other viruses are more complex and have an outer phospholipid, cholesterol, glycoprotein, and glycolipid envelope that is derived from virus-modified infected cell membranes. Cell nuclear, endoplasmic reticulum, Golgi, or plasma membranes that become parts of the viral envelope have usually been modified during infection by the insertion of virus-encoded glycoproteins, which mediate contact of enveloped virus with uninfected cell surfaces. Matrix or tegument proteins may fill the space between the nucleocapsid and the outer envelope of the virus.

Enveloped viruses are usually sensitive to lipid solvents or detergents that can dissolve the envelope, whereas viruses with protein nucleocapsid exteriors may be somewhat detergent resistant. A schematic diagram of large and complex herpesviruses is shown in Fig. 214e-1. Structures of prototypical pathogenic human viruses are described in Table 214e-1. The relative sizes and structures of typical pathogenic human viruses are shown in Fig. 214e-2.

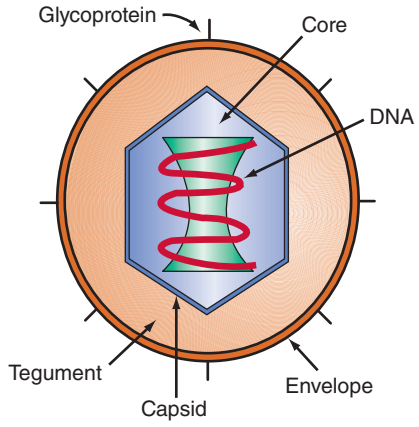

FIGURE 214e-1 Schematic diagram of an enveloped herpesvirus with an icosahedral nucleocapsid. The approximate respective dimensions of the nucleocapsid and the enveloped particles are 110 and 180 nm. The capsid is composed of 162 capsomeres: 150 with sixfold and 12 with fivefold axes of symmetry.

TAXONOMY OF PATHOGENIC HUMAN VIRUSES

As is apparent from Table 214e-1 and Fig. 214e-2, the classification of viruses into orders and families is based on nucleic acid composition, nucleocapsid size and symmetry, and presence or absence of an envelope. Viruses of a single family have similar structures and may be morphologically indistinguishable in electron micrographs. Subclassification into genera depends on similarity in epidemiology, biologic effects, and nucleic acid sequence.

Most viruses that infect humans have a common name related to their pathologic effects or the circumstances of their discovery. In addition, formal species names—consisting of the name of the host followed by the family or genus of the virus and a number—have been assigned by the International Committee on Taxonomy of Viruses. This dual terminology can cause confusion when viruses are referred to by either name—e.g., varicella-zoster virus (VZV) or human herpesvirus 3 (HHV-3).

VIRAL INFECTION IN VITRO

STAGES OF VIRAL INFECTION OF CELLS IN CULTURE

Viral Interactions with Cell Surfaces and Cell Entry To deliver its nucleic acid payload to the cell cytoplasm or nucleoplasm, a virus must overcome barriers posed by the cell's plasma and cytoplasmic membranes. Infection is frequently initiated by weak electrostatic or hydrophobic interactions with the cell surface. Subsequent stronger, more specific attachment to a cell plasma membrane protein, carbohydrate, glycolipid, heparan sulfate proteoglycan, or sialic acid enables stable binding to a specific cell surface "receptor" that mediates fusion with the cell plasma membrane (see Table 145e-1). Receptor binding is often augmented by a viral surface protein interaction with more than one cell surface protein or co-receptor. Receptors and co-receptors are important determinants of the species and cell type that a virus can infect. For example, the HIV envelope glycoprotein binds to the T cell surface protein CD4 and then engages a chemokine receptor that is the definitive co-receptor for the virus and mediates entry into the cell cytoplasm. The Epstein-Barr virus (EBV) glycoprotein gp350 binds to the B lymphocyte complement receptor CD21 and then uses a major histocompatibility complex (MHC) class II molecule as a co-receptor and an integrin for definitive entry.