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Chapter 2

Basics of virology

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INTRODUCTION

Viruses and virus infections of the nervous system have shaped human history for millennia. Egyptian hieroglyphics depict withered legs typical of poliomyelitis, Mesopotamians had laws relating to control of rabid dogs, and Homer described Hector as rabid in the *Iliad*. The first vaccines were generated against viruses (variola by Jenner and rabies by Pasteur). Development of vaccines against poliovirus by Sabin and Salk was enabled by development of methods for propagation of viruses in cultured cells by Enders, Weller, and Robbins. Here we describe the fundamental principles of virology in the context of viruses of neurologic importance.

WHAT IS A VIRUS?

The word "virus" is derived from the Latin word for poison. Viruses are associated with all forms of life (bacteria, archaea, and eukaryotes). Viruses are infectious, obligate intracellular parasites whose genomes consist of either DNA or RNA. Virus genomes direct their own replication and the synthesis of other viral components, using cellular systems in appropriate host cells. Virus particles (known as virions) are formed by assembly from newly synthesized components within the host cell. Virions are the vehicle for transmission of the genome to the next host cell or organism, where their disassembly initiates the beginning of the next infectious cycle. A minimal virus consists of a genome that has an origin of replication, plus a proteinaceous coat, known as a capsid. For enveloped viruses, the capsid is enclosed in a host cell-derived lipid bilayer studded with virus-specified glycoproteins. Viruses are dependent on host cells for biosynthesis of proteins and other critical macromolecules.

VIRUS TAXONOMY AND NOMENCLATURE

Taxonomy is a relational discipline that classifies organisms according to shared and distinguishing properties. The various virus lineages appear to have independent evolutionary origins, thus there is no overriding phylogeny for viruses. The two major classification schemes used for viruses are the comprehensive formal taxonomy developed over the past 40-plus years under the aegis of the International Committee for Taxonomy of Viruses (ICTV), and a scheme developed by David Baltimore (the Baltimore system) in which viruses are grouped on the basis of the path from their genome type to production of translatable mRNA. The ICTV system will be discussed in this section and the Baltimore system will be discussed in the section on virus replication cycles.

Within the ICTV system (King et al., 2011), the two major taxonomic divisions are the viruses with RNA genomes and those with DNA genomes. Subsequent taxonomic levels are based on the size and structure of the capsid (icosahedreal, helical, or complex), whether the capsid is enveloped, and then the nature of the genome (single-stranded or double-stranded, linear or circular, segmented or non-segmented). This information is sufficient to define the major groups of genetically distinct viruses into families, with some families being grouped

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into orders. Families are subdivided into genera, which are collections of related but distinct virus species. Some large families are divided into subfamilies that are then divided into genera. Subfamilies, genera, and species are defined by properties such as gene organization, replication mechanism, susceptibility to physical stresses and chemical agents, cell tropism, and immunologic and pathogenic properties.

As defined by ICTV, "A virus species is a polythetic class of viruses that constitutes a replicating lineage and occupies a particular ecological niche." The distinct epidemiologic or biologic characteristics of members of a virus species define its "particular ecological niche."

Within the ICTV nomenclature system, orders are given the suffix "-virales," families use "-viridae", subfamilies use "-virinae", and genera use "-id." Virus species names are italicized. In some instances, widely used common names differ from their formal designation, e.g., polioviruses are formally assigned to the species *Human enterovirus C*.

Two examples:

1. Family Orthomyxoviridae, genus *Influenzavirus A,* species *Influenza A* (common name, influenza A virus).
2. Order Herpesvirales, family Herpesviridae, subfamily Alphaherpesvirinae, genus *Simplexvirus*, species *Human herpesvirus 1* (common name, herpes simplex virus 1 (HSV-1)).

VIRION STRUCTURE

Virions are the infectious form of viruses, and exist to protect the virus genome during its journey to, and to facilitate its entry into, a susceptible cell (Prasad and Schmid, 2012). Virions contain the virus genome and proteins that form the capsid that protects the genome (Fig. 2.1). For some viruses, the genome-containing capsid is enclosed in an envelope, which is a lipid bilayer membrane derived from either the host cell plasma membrane or the membrane of an intracellular vesicle. Virion envelopes contain one or more species of virus-specified membrane glycoprotein. Depending on the virus and the complexity of its virion, additional constituents can include mRNAs, proteins that are carried in the space between the capsid and the envelope, and small molecules such as polyamines. Although many virion substructures can self-assemble from purified components, virions are highly organized structures whose construction results in reduced entropy and therefore requires energy. As part of its incorporation into virions, the negatively charged phosphodiester backbone of the virus genome needs to be neutralized, through the use of positively charged amino acids in genome-interacting capsid proteins (nucleoproteins) or by polyamines or other small cationic molecules. Virion assembly involves coordinated manufacture and transport of virion components (e.g., virion proteins and newly replicated virus genomes) to appropriate intracellular locations where the several steps of virion assembly can take place. In addition to needing to be efficiently assembled and to withstand environmental stresses, virions ultimately need to disassemble in an appropriately regulated manner after entry into a newly infected cell.

Capsids come in two main forms, icosahedral and helical, and range widely in size and complexity (Fig. 2.1). Icosahedral capsids are formed from triangular subunits that are built from one or more virus capsid proteins. Parvovirus capsids are relatively small and less complex icosahedra, 18–26 nm in diameter, built from a total of 60 molecules of three variants of the single virion protein. In contrast, herpesvirus capsids are icosahedra of ~100 nm diameter, built from >1900 individual protein molecules (Fig. 2.1). Helical capsids are formed from nucleoproteins that coat helices of virus genomes to form helical cylinders whose diameter is determined by the size and structure of the capsid protein, and whose length is a function of the length of the virus genome (Fig. 2.1, rhabdovirus).

Virions can have significant biologic activities beyond delivery of infectious payloads from cell to cell and organism to organism. The act of a virion binding to its cellular receptor can trigger a wide range of rapid (within seconds or minutes) host cell responses, including antiviral responses and dramatic cytoskeletal rearrangements. Virion proteins can play roles in modulating intrinsic responses to viral nucleic acids and in managing host transcriptional machinery to support virus reproduction better. For some viruses, important enzymes needed for virus genome replication are included in the virion, such as the RNA-dependent RNA polymerases (RdRp, sometimes referred to as RNA transcriptases) that are absolutely essential for generating mRNAs from negative-strand RNA virus genomes.

Virus genomes can be categorized according to the form of the nucleic acid. Most RNA virus genomes are linear. They can be single-stranded in the orientation that enables direct protein translation (plus-strand genomes, or ssRNA+), single-stranded in the orientation antisense to protein translation (negative-strand genomes, or ssRNA–), and double-stranded (dsRNA). DNA virus genomes can be single-stranded or double-stranded (ssDNA and dsDNA), and circular or linear. Most of the genomic length of viruses is used to encode proteins. Some single-stranded RNA virus genomes encode proteins that are expressed from the plus strand and other proteins that are expressed from the complementary minus strand (ambisense genomes of arenaviruses and bunyaviruses). Individual genes of some

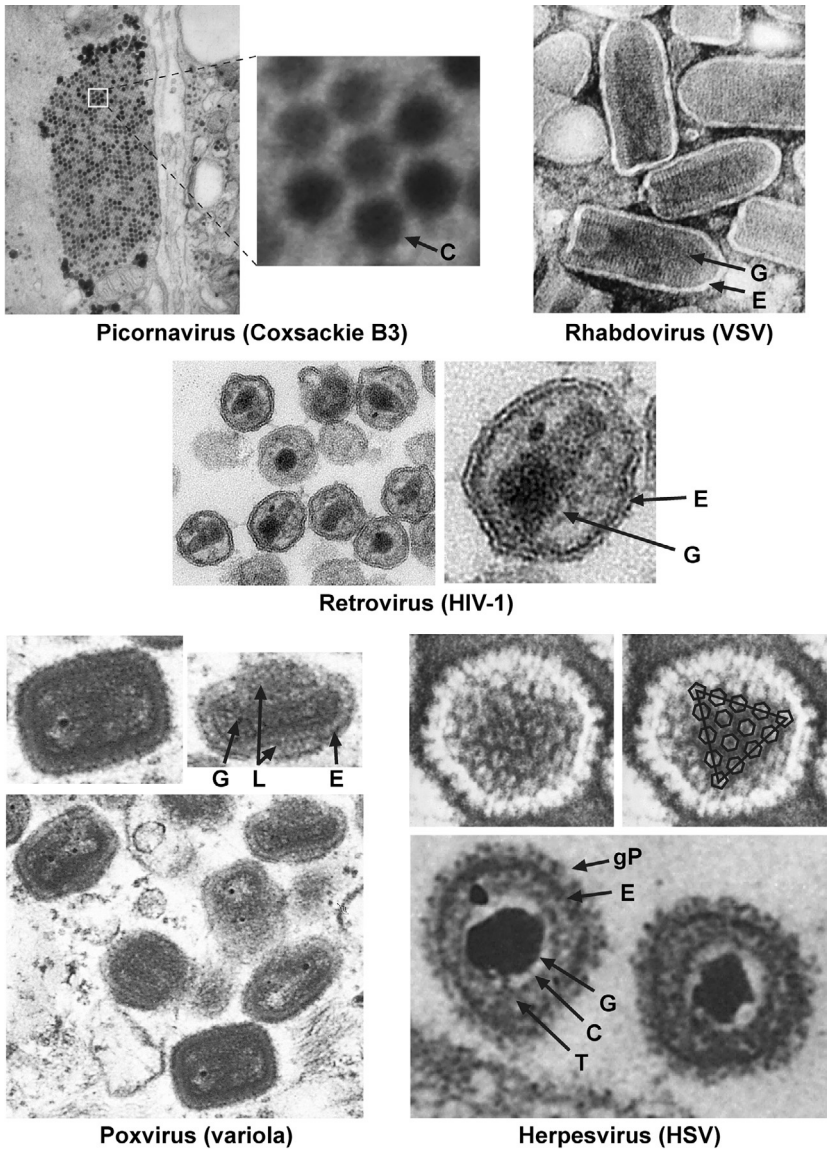

Fig. 2.1. Virion ultrastructure gallery. Top left: Paracrystalline array of Coxsackie B3 virus virions (a picornavirus of genus *Enterovirus*) virions in muscle tissue. A close-up of seven virions is shown in the enlargement. The nearly spherical non-enveloped icosahedral capsids are 28–30 nm in diameter. Public Health Image Library (PHIL) image ID# 10204. Top right: Virions of vesicular stomatitis virus (VSV), a rhabdovirus with bullet-shaped virions of approximately 80 nm in diameter that are similar in appearance to those of rabies virus. Striations from the helically packed genome are visible inside the enveloped virions. PHIL ID# 5611. Center: Virions of the retrovirus human immunodeficiency virus (HIV)-1. The enveloped virions are 80–100 nm in diameter, and contain an outer matrix and an inner capsid that houses the virus genome. PHIL ID# 13472. Lower left: Variola (smallpox) virus virions (Poxviridae). Virion lengths range from 220 to 450 nm and widths and thicknesses from 140 to 260 nm. The genome-containing core is surrounded by proteinaceous lateral bodies and an envelope containing non-glycosylated virus-encoded membrane proteins. PHIL ID# 2291. Bottom right: Herpesvirus. The upper panels show a herpes simplex virus (HSV) capsid (upper panels), with the locations of the capsomeres on one icosahedral face being outlined in the image on the right. PHIL ID# 10230. The lower image of an infected tissue shows two enveloped extracellular virions (diameter of 150–180 nm) PHIL ID# 10260. C, capsid; E, envelope; gP, glycoprotein spike; L, lateral body; T, tegument; G, genome.

The Coxsackie B3 virus, variola virus, and HSV images were obtained by Fred Murphy and Sylvia Whitfield, the rhabdovirus image by Fred Murphy, and the HIV image by Maureen Metcalfe and Tom Hodge.

viruses are encoded on independent genome molecules that are analogous to independent chromosomes (segmented genomes of orthomyxoviruses). Protein coding genes of viruses come in several forms. For some, a single large open reading frame (ORF) is translated into a large polyprotein that is subsequently proteolytically processed into multiple independent proteins. For many others, multiple ORFs are translated into individual proteins. Many viruses express non-coding RNAs, such as microRNAs. In addition to the sequences involved in producing *trans*-acting products such as proteins and non-coding RNAs, virus genomes have regions that serve as signals for, and play structural roles in, virus replication and packaging into capsids.

VIRUS ORIGINS AND EVOLUTION

Virus origins

Viruses likely originated by several mechanisms during the history of life. The "RNA world" hypothesis posits the existence of self-replicating RNAs that eventually developed into cellular organisms. Parasitic RNAs surely existed during this period. Of existing genetic parasites, viroids may be nearest to these agents. Certain viruses may also trace their origins to intracellular DNA elements, such as transposons, that acquired an extracellular phase. Other viruses (e.g., poxviruses) may also have originated by regressive evolution of microorganisms.

Virus and host coevolution

Viruses apply evolutionary pressures to their hosts and are themselves influenced in return. An excellent example is provided by the herpesviruses. There is a high level of congruence between the phylogenetic trees of mammalian herpesviruses and their hosts, indicating coevolution over many millions of years. Retroviruses have influenced host evolution in an especially direct manner. Integration of retroviral proviruses into germline DNA can lead to permanent residence of the virus genome in the host genome; as much as 8% of the human genome originated from retroviruses. Integrated defective proviruses may interfere with non-defective viruses, providing a survival benefit to the host.

Mechanisms of mutation

Base substitution mutations are a major mechanism of virus evolution. Rates of such mutation vary widely among viruses. dsDNA viruses (Baltimore class I; see Fig. 2.3, below) have mutation rates on the order of 10^{-7} per nucleotide per year, ~10-fold higher than their hosts. Mutation rates for RNA viruses are much higher, on the order of 10^{-3} per nucleotide per year. This is primarily due to the proofreading ability of the DNA polymerases, whether host or viral, that replicate class I viral genomes. The RdRp of RNA viruses lack proofreading ability. Further, ssRNA virus genomes lack the information redundancy of double-stranded genomes.

Virus genomes may also evolve by recombination and reassortment, which can give rapid rise to viruses with novel properties. Recombination rates for human immunodeficiency virus-1 (HIV-1) may be even higher than the base substitution rate. Reassortment is a major evolutionary mechanism for viruses with segmented genomes. This is particularly important for influenza viruses, where antigenic shift resulting from reassortment can give rise to pandemic strains. Reassortment has also been noted among the Reoviridae.

Evolution in the host

Virus evolution also occurs within individual hosts during the course of infection. In many HIV-1-infected individuals, the coreceptor preference evolves from CCR5 during the acute phase to CXCR4 during the later chronic phase. During progressive multifocal leukoencephalopathy (PML), JC virus isolates from cerebrospinal fluid and peripheral blood leukocytes have rearranged transcriptional control regions compared to the prototype form of the virus. In addition to these apparently host-driven selections, acquisition of resistance to antiviral drugs occurs. Finally, it should be noted that viruses accumulate unselected genomic changes during the course of replication in individual hosts. This is especially the case for RNA viruses, with their high rate of nucleotide substitution.

VIRUS REPLICATION CYCLES

Overview

Although virus replication is intimately connected to cellular processes, viruses are acellular genetic parasites that use cells to provide the systems and resources necessary for their replication. Virions are sophisticated devices for delivery of the viral genome to suitable host cells. The wide diversity of virus genome types and virion structures leads to a great diversity of virus replication schemes. While much remains to be learned, great progress has been made in understanding the replicative mechanisms of most clinically important viruses (Flint et al., 2009; King et al., 2011; Knipe et al., 2013).

Entry

The virus replication cycle begins with entry of the virus into the host cell. This stage comprises several steps: attachment, penetration, and uncoating (Fig. 2.2). Attachment proteins on the virion surface recognize and bind to specific receptors on the cell surface.

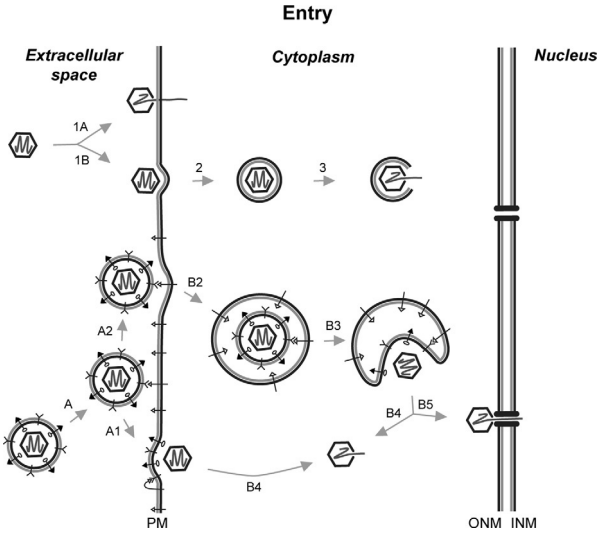

Fig. 2.2. Major paths of virion entry. The major paths for entry of non-enveloped virions are direct injection of the genome across the plasma membrane (1A) and via an endocytic pathway (1B) that involves receptor (not shown)-mediated uptake into an endocytic vesicle (2), followed by intracytoplasmic release of the virion and the genome (3). Enveloped virions interact with a cell surface receptor (A), and either enter by membrane fusion at the plasma membrane (A1) or by uptake of the virion into an endocytic vesicle (A2 to B2), followed by fusion of the virion envelope with the vesicle membrane (B3), releasing the capsid into the cytoplasm. Some viruses release their genome directly into the cytoplasm (B4). Herpesvirus capsids dock with nuclear pores and then inject their genomes into the nucleus (B5). INM, inner nuclear membrane; ONM, outer nuclear membrane; PM, plasma membrane.

In the case of enveloped virions, attachment is usually mediated by a specific virus envelope glycoprotein, e.g., the influenza virus hemagglutinin glycoprotein (Cosset and Lavillette, 2011). For non-enveloped viruses, attachment may be mediated by a single protein, such as the adenovirus fiber protein, or by a multiprotein structure as for poliovirus (Moyer and Nemerow, 2011; Suomalainen and Greber, 2013). Penetration is the process by which the virus gains access to the cytoplasm. Envelopes of some viruses, e.g., HIV-1, fuse directly with the cellular plasma membrane. Other enveloped viruses, e.g., influenza viruses, are endocytosed and ultimately fuse their envelopes with the endocytic vesicle membrane. In both mechanisms, a conformational change in a viral membrane protein exposes a hydrophobic fusion peptide that triggers membrane fusion, releasing the virus nucleocapsid into the cytoplasm (Plemper, 2011). Penetration mechanisms of non-enveloped viruses are less well understood than for enveloped viruses. Interaction of non-enveloped viruses with the cell surface or endocytic vesicles leads to conformational changes that expose a hydrophobic domain or other membrane-destabilizing structure. In a number of instances, triggering the conformational changes involved in penetration requires a cellular coreceptor or a change in virion environment, such as acidification of an endocytic compartment.

Further changes to the virion must take place to allow the virus genome to access cellular components necessary for viral replication. Details of this uncoating process depend on virus type and replication strategy and the compartment within the cell where virus genome replication occurs. For most DNA viruses (Baltimore classes I and II, poxviruses excepted; see Fig. 2.3, below), the genome-containing capsid or nucleoprotein complex is transported to the vicinity of a nuclear pore, followed by delivery of the genome through the pore to allow initiation of gene expression and replication. For positive-strand RNA viruses (Baltimore class IV), dissociation of the genomic RNA from the capsid allows it to associate with ribosomes, beginning viral gene expression. For double-stranded and negative-strand RNA viruses (Baltimore classes III and V), uncoating typically removes the outer components of the virion but leaves the genome associated with the virus-encoded RdRp.

Gene expression

After entry, virus genes must be expressed (transcribed to mRNA and translated) for the replication cycle to continue. Although virus genome types and gene organization vary widely, the central importance of mRNA production has been used to develop a robust classification scheme for viruses. In essence, the type and structure of a virus's genetic material dictate key aspects of its gene expression scheme. The critical virus genome characteristics are the type of nucleic acid (DNA or RNA), whether it is single-stranded (ss) or double-stranded (ds), and, for single-stranded RNA, whether it is positive or negative sense (+ or −) (Flint et al., 2009; Knipe et al., 2013).

Most of the DNA viruses that infect humans have dsDNA genomes and fall into Baltimore class I. Parvoviruses, such as B19 virus, have single-stranded DNA genomes and are members of class II. With the exception of the poxviruses, all the human-infecting DNA viruses replicate their genomes in the nucleus and use cellular RNA polymerase II to transcribe their protein-encoding genes. Primary RNA transcripts produced by the nuclear-replicating DNA viruses are processed into mRNAs and transported to the cytoplasm for translation. mRNA transport pathways are sometimes modified by viral proteins. Poxviruses are unique among the DNA viruses in replicating their genomes in the cytoplasm, which requires them to encode their own RNA

polymerase for transcription of mRNAs. RNA viruses fall into classes III–VI. With the exception of the retroviruses (class VI), which replicate through a DNA intermediate, the RNA viruses encode RdRp for mRNA production, since mammalian cells lack enzymes able to produce RNA from RNA templates. Retroviruses encode an RNA-dependent DNA polymerase (reverse transcriptase) to produce a DNA provirus from their RNA genomes. After integration of the provirus into host DNA, viral mRNAs are transcribed by host RNA polymerase II. Hepatitis B virus (class VII) has a dsDNA genome that passes through an RNA replicative intermediate that must be reverse transcribed to produce new genomes.

Due to their small genomes, viruses use several strategies to maximize the coding potential of their genomes, including overlapping genes and alternative splicing, which allow more than one mRNA, and thus more than one protein, to be produced from a single genomic region. Viruses may also make use of alternative initiation codons, internal ribosomal entry sites, or translational frameshifting to produce multiple proteins from a single mRNA.

Genome replication

The Baltimore classification system (Fig. 2.3) provides insight into viral replication mechanisms as well as mRNA production, since viruses within each group use similar strategies to replicate their genomes (Flint et al., 2009; Knipe et al., 2013). Except for the poxviruses, DNA viruses replicate their genome-infected cell nuclei. Class I (dsDNA) viruses replicate their genomes via mechanisms similar to host cell DNA replication. The

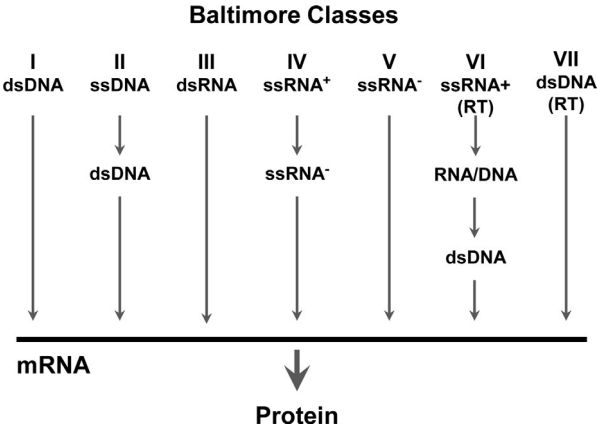

Fig. 2.3. Baltimore classification of virus genomes. This classification scheme categorizes all known viruses into seven classes based on their genome type and the consequent path to production of mRNA, which is required for translation of viral proteins.

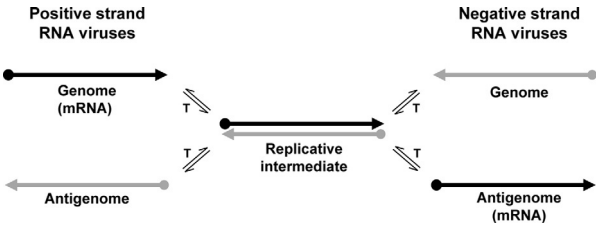

Fig. 2.4. Replication of ssRNA virus genomes. ssRNA+ and ssRNA– genomes must be transcribed (T) by the viral RdRp to form the dsRNA-replicative intermediate. The resulting antigenomes can then be transcribed by the RdRp to form replicative intermediates that can yield additional genome RNAs. Regulated asymmetries in transcription initiation enable production of appropriate quantities of genome and antigenome strands at different stages of virus replication. ssRNA+ genomes and ssRNA– antigenomes have polarities suitable for translation of viral proteins. Viruses employ a variety of mechanisms to generate 5' structures that enable some RNA+ molecules to function as mRNAs. RNA+ molecules are drawn in black and RNA– molecules are in gray. Balls on the ends of RNAs signify 5' ends, and arrows signify 3' ends.

smaller DNA viruses utilize cellular enzymes for this process while viruses with larger genomes encode their own DNA replication enzymes. Class II (ssDNA) viruses, with small single-stranded DNA genomes, employ cellular enzymes to synthesize a dsDNA replication intermediate, from which ssDNA progeny genomes are produced. With the exception of the orthmyxoviruses and retroviruses, RNA viruses replicate their genomes in the cytoplasm. Class IV (ssRNA+) viruses have genomes that can function as mRNAs and are translated directly into a polyprotein upon uncoating of the virus genome. Autocatalytic cleavage of the polyprotein releases the viral RNA-dependent RNA polymerase, which then transcribes the full-length complementary RNA copies of the genome (antigenomes) that are used as templates for synthesis of progeny genomes (Fig. 2.4). Although single-stranded, the genomes of class V (ssRNA–) viruses cannot be translated directly upon uncoating because the genome is antisense to the protein coding region. Virions of these viruses, as well as class III (dsRNA) viruses, contain a virus-encoded RdRp that transcribes the virus genome to produce mRNAs as well as full-length complementary copies of the genome that serve as templates for the production of progeny genomes (Fig. 2.4).

Assembly and egress

Virion assembly involves many moving parts and extensive interaction with cellular machinery for protein processing and transport (Fig. 2.5) (Flint et al., 2009; Knipe et al., 2013). Typically, nascent virions, or at least

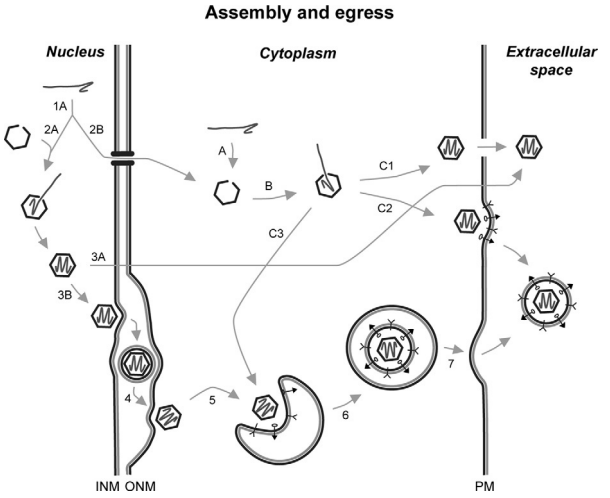

Fig. 2.5. Major paths of virion entry, assembly, and egress. For some viruses, capsids are formed in the nucleus and, for others, capsids are formed in the cytoplasm. Some nuclear replicated genomes are transported from the nucleus to the cytoplasm for packaging into capsids that assemble in the cytoplasm (1A and 2B), joining the egress pathway of virions whose genomes and capsids are produced in the cytoplasm. Cytoplasmically replicated genomes are packaged into cytoplasmically assembled capsids (A and B). These filled capsids can then make their way out of the cell via cell lysis (C1), acquisition of and envelope during budding from the plasma membrane (C2), or by budding into a cytoplasmic vesicle that ultimately fuses with the plasma membrane and releases the enveloped virion (C3, 6, and 7). For some viruses with nuclear replicated genomes that fill nuclear assembled capsids (2A), virions can make their way out of the cell after cell lysis (3A). Filled herpesvirus capsids acquire an envelope during budding into the lumen of the nuclear membrane. This envelope fuses with the outer nuclear membrane, releasing a naked capsid into the cytoplasm (3B and 4). In the cytoplasm, the filled capsid buds into a cytoplasmic vesicle for transport to the plasma membrane for release of the re-enveloped virion (5–7). INM, inner nuclear membrane; ONM, outer nuclear membrane; PM, plasma membrane.

capsids, are assembled in the cellular compartment where genome replication takes place. Thus, most RNA viruses assemble in the cytoplasm, and most DNA viruses at least begin assembly in the nucleus. Non-enveloped virions are generally released during lysis of infected cells. For enveloped virions, assembly of a genome-containing capsid is followed by budding through the appropriate cellular membrane to acquire an envelope. This may be the plasma membrane, in which case this final assembly step actually releases the virion from the cell, or it may be the nuclear, endoplasmic reticulum, Golgi, or other organelle membrane. Subsequently, the nascent virion is transported in a vesicle to the plasma membrane for release from the cell by fusion of the vesicle with the plasma membrane.

NEUROTROPIC VIRUSES

dsDNA viruses (Baltimore class I)

Herpesviruses

Family *Herpesviridae* includes over 80 viruses distributed among three subfamilies: Alpha-, Beta-, and Gammaherpesvirinae (King et al., 2011). Three human viruses are members of the *Alphaherpesvirinae*: HSV-1 and HSV-2 (genus *Simplexvirus*), and varicella-voster virus (VZV; genus *Varicellovirus*). Human *Betaherpesvirinae* include human cytomegalovirus (HCMV; genus *Cytomegalovirus*), human herpesviruses 6A and 6B (HHV-6A and -6B; genus *Roseolovirus*), and human herpesviruses 7 (HHV-7; genus *Roseolovirus*). Of the *Gammaherpesvirinae*, humans are hosts to Epstein–Barr virus (EBV; genus *Lymphocryptovirus*) and human herpesvirus 8 (HHV-8 or Kaposi's sarcoma-associated herpesvirus; genus *Rhadinovirus*).

Infection of the nervous system is an integral part of the survival strategy of alphaherpesviruses. These viruses are neurotropic and establish latent infections in ganglionic neurons during primary infection, subsequently reactivating to cause recurrent disease or subclinical virus shedding, promoting spread to new hosts (Nicoll et al., 2012). Associated diseases include peripheral neuropathies such as postherpetic neuralgia, Bell's palsy, and potentially life-threatening encephalitis (Table 2.1). Although the viruses in the other subfamilies are less neurotropic, these viruses can also cause neurologic disease.

Herpesvirus virions are large (120–180 nm) enveloped particles (Fig. 2.1). The envelope encloses an icosahedral capsid that contains the viral genome. The tegument, a proteinaceous structure unique to the herpesviruses, lies between the capsid and envelope. Herpesviruses have large dsDNA genomes (123–230 kb) that encode 70–200 proteins, most of which are expressed from independent transcriptional units that can found on either strand of the genome.

Initial attachment of most human herpesviruses is to heparan sulfate moieties on cell surface proteoglycans; EBV attaches to cell surface CD21 and major histocompatibility complex (MHC) class II glycoproteins and HHV-6 employs CD46 as a receptor (Eisenberg et al., 2012). Depending on cell type, entry can be via direct fusion of the virion envelope with the plasma membrane or by an endocytic route (Fig. 2.2, paths A1 and A2). After transport of the capsid to nuclear pores and injection of the genome into the nucleus, virus genes are transcribed in several phases by host RNA polymerase II. Immediate early-phase genes adapt the cell for virus replication, early genes carry out viral DNA replication, and late genes encode viral structural proteins as well as

Table 2.1

Viruses associated with neurologic diseases of humans

Taxonomic group	Virus	Disease associations	
		Non-neurologic	Neurologic
ds DNA (Baltimore class I)			
Herpesviridae	Herpes simplex viruses 1 and 2	HSV-1: fever, gingivostomatitis	Encephalitis, Bell's palsy
Alphaherpesvirinae		HSV-2: genital lesions	
	Varicella-zoster virus	Varicella (chickenpox), zoster (shingles)	Zoster, encephalitis, postherpetic neuralgia, Bell's palsy, transverse myelitis
Betaherpesvirinae	Cytomegalovirus	Mononucleosis, congenital infection, pneumonitis, retinitis	Encephalitis, learning disabilities, hearing and vision loss, Guillain–Barré' syndrome, myelitis
	Human herpesviruses 6A and 6B	HHV-6A: Hashimoto's thyroiditis HHV-6B: roseola (exanthem subitum)	HHV-6B: febrile convulsions, epileptic seizures and febrile status epilepticus, encephalitis, posttransplant limbic encephalitis and cognitive dysfunction
Gammaherpesvirinae	Epstein–Barr virus	Infectious mononucleosis, Burkitt lymphoma, nasopharyngeal carcinoma, lymphoproliferative disease (immunocompromised)	Encephalitis, CNS lymphomas
	Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8)	Kaposi's sarcoma	CNS lymphomas
Polyomaviridae	JC virus		Progressive multifocal leukoencepahalopathy
Poxviridae	Monkeypox virus	Monkeypox	Headache
	Vaccinia virus		Postvaccination encephalomyelitis
	Variola virus	Smallpox	Encephalitis
ds RNA (Baltimore class III)			
Reoviridae	Colorado tick fever Virus	Colorado tick fever (tickborne)	Headaches, aseptic meningitis, and encephalitis
ss RNA + (Baltimore class IV)			
Coronaviridae	SARS coronavirus	Acute respiratory distress	Axonopathic polyneuropathy, myopathy, and ischemic stroke
Flaviviridae	Tick-borne encephalitis virus		Meningitis, meningoencephalitis, poliomyelitis-like flaccid paralyisis, and polyradiculoneuritis (Europe)
	Dengue virus	Dengue hemorrhagic fever/ Dengue shock syndrome	Meningitis, meningoencephalitis, polyneuritis, parkinsonian symptoms
	Japanese encephalitis virus		Aseptic meningitis, meningoencephalitis, flaccid paralysis, and encephalitis, parkinsonian symptoms (Asia)
	St. Louis encephalitis virus		Viral encephalitis (North America)

	Murray Valley virus		Viral encephalitis
	West Nile virus	Flu-like illness, arthritis, hepatitis, pancreatitis, myocarditis	Encephalitis, meningitis, acute flaccid paralysis, seizures, cerebellar ataxia.
	Hepatitis C virus	Acute/chronic hepatitis C infection, cirrhosis, hepatocellular carcinoma, cryoglobulinemia, membranoproliferative glomerulonephritis	Peripheral neuropathy
Picornaviridae	Poliovirus types 1, 2, and 3		Acute flaccid paralysis
Enterovirus	Human enteroviruses A–D	Respiratory infections, hand, foot, and mouth disease, herpangina, Bornholm disease, pleurodynia	Aseptic meningitis, brainstem encephalitis, acute flaccid paralysis
	Rhinovirus	Common cold, lower respiratory tract infection	
Hepatovirus	Hepatitis A virus	Acute viral hepatitis	Encephalitis
Parechovirus	Human parechovirus	Mild gastrointestinal or respiratory illness	Aseptic meningitis, meningoencephalitis, and neonatal encephalitis
Togaviridae	Eastern equine encephalitis virus	Moderate to severe illness	Viral encephalitis
Alphavirus	Venezuelan equine encephalitis virus	Flu-like illness	Viral encephalitis
	Western equine encephalitis virus	Mild to moderate illness, pneumonitis	Viral encephalitis
Rubivirus	Rubella virus	German measles	Congenital rubella syndrome
ss RNA- (Baltimore class V)			
Arenaviridae	Lassa virus	Lassa fever	Encephalopathy
	Lymphocytic choriomeningitis virus		Aseptic meningitis, hydrocephalus
	California encephalitis virus		Encephalitis
Bunyaviridae	La Crosse virus		Encephalitis
	Hanta virus	Hemorrhagic fever with renal syndrome, Hanta virus pulmonary syndrome	Acute disseminated encephalomyelitis, transverse myelitis
	Sin nombre virus	Respiratory infection	
	Crimean-Congo hemorrhagic fever virus	Hemorrhagic fever	
Orthomyxoviridae	Influenza A, B, and C viruses	Pneumonia, myositis	Encephalitis, transverse myelitis, stroke
Paramyxoviridae	Mumps virus	Mumps	Encephalitis, transverse myelitis
	Measles virus	Measles	Encephalitis, subacute sclerosing panencephalitis
Rhabdoviridae	Rabies virus		Encephalitis, paralytic rabies
ss RNA (RT) (Baltimore class VI)			
Retroviridae	HIV-1	Acute retroviral syndrome, AIDS	HIV-associated dementia, mild neurocognitive disorder, aseptic meningitis, multiple sclerosis-like disorders
	HTLV-1	Adult T-cell leukemia/lymphoma, uveitis, infective dermatitis, polymyositis	Tropical spastic paraparesis/HTLV-1-associated myelopathy

AIDS, acquired immunodeficiency syndrome; CNS, central nervous system; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HTLV, human T-lymphotropic virus; SARS, severe acute respiratory syndrome.

non-structural proteins essential for assembly and egress. Assembly and egress of the progeny virions are complex, involving capsid assembly in the nucleus, envelopment at the inner nuclear membrane (Fig. 2.5, path 1A/3B), followed by de-envelopment at the outer nuclear membrane and acquisition of a final envelope by budding through cytoplasmic membranes (Mettenleiter et al., 2009; Johnson and Baines, 2011). Secretory vesicles containing viral particles fuse with the plasma membrane, releasing the virions from the cell.

Primary HSV-1 infection is commonly associated with gingivostomatitis, although it is most often asymptomatic. The virus enters nerve cells innervating the site of primary infection and viral capsids are transported to the nerve cell body in the peripheral ganglion, where latency is established (Nicoll et al., 2012). Latent virus reactivates intermittently, resulting in limited ganglionic replication and transport of virus down the axon, causing virus shedding and sometimes recurrent lesions near the site of the original infection. HSV-2 infections resemble those of HSV-1 but typically are sexually transmitted and affect the genitals and surrounding areas. In rare instances, HSV-1 may cause encephalitis and has been associated with Bell's palsy (Michael and Solomon, 2012). HSV encephalitis may be associated with primary neonatal infection or may occur later in life as a form of recurrent disease (Corey and Wald, 2009). In the absence of antiviral therapy, mortality is >70%. Survival is dramatically improved by antiviral therapy, but survivors may have serious neurologic sequelae.

VZV is transmitted via respiratory aerosols. Primary infection of unvaccinated individuals results in varicella (chickenpox). After replication in the respiratory tract and lymphoid organs, viremic transmission to the skin results in characteristic vesicular lesions. Central nervous system (CNS) complications of varicella are infrequent (~1–3 occurrences per 10 000 cases), with encephalitis and cerebellar ataxia being most frequent. Transverse myelitis, meningitis, and Guillain–Barré syndrome have also been reported (Hung et al., 2012). VZV enters nerve cells innervating infected areas and establishes latency in dorsal root and trigeminal ganglia (Gilden et al., 2011). Decades after primary infection, VZV may reactivate to cause zoster (shingles). The rash is often preceded by a prodromal "pins-and-needles" sensation and by non-specific symptoms such as fever and headache. Although the duration of the rash is typically 2–4 weeks, some patients suffer from postherpetic neuralgia that may last for months or years. VZV reactivation is sometimes associated with Bell's palsy-like symptoms (Ramsay Hunt syndrome type 2). CNS complications of VZV reactivation include encephalitis with extensive lymphocyte infiltration and vasculitis, as well as transverse myelitis.

HCMV is among the most prevalent human pathogens (Griffiths, 2012). Primary infection during childhood is most often mild or asymptomatic. When acquired later in life, a mononucleosis-like condition may occur. Neurologic disease is most likely to occur as a result of congenital CMV infection and in immune-compromised individuals (Bale, 2012). Congenitally infected infants who survive may develop long-term neurologic problems, including mental retardation, deafness, visual impairments, and other physical problems. Immune-compromised persons may experience a range of neurologic complications from primary or reactivated CMV infections, including encephalitis, myelitis, and retinitis.

Primary EBV infection most often occurs during childhood and is asymptomatic or associated with pharyngitis and other mild, non-specific symptoms. Primary infection during adolescence or adulthood is often associated with mononucleosis, which is sometimes associated with Bell's palsy. Encephalitis associated with EBV infection has been described, but is rare (Volpi, 2004). EBV is almost always associated with CNS lymphomas that occur in immunocompromised patients, and an etiologic role for the virus in multiple sclerosis continues to be discussed (Owens and Bennett, 2012; Tselis, 2012).

HHV-6A, HHV-6B, and HHV-7 are closely related but have distinct properties (Flamand et al., 2010). These viruses are virtually ubiquitous and are most often acquired during childhood. Primary HHV-6B infection causes most cases of exanthem subitum (roseola or sixth disease), a common childhood febrile illness; in severe cases, convulsions or seizures may occur. Exanthem subitum may also result from primary HHV-7 infection. HHV-6B is frequently present in cerebrospinal fluid (CSF) during primary infection (Yao et al., 2010). Although the frequency of detecting HHV-6A in CSF is lower than for HHV-6B, HHV-6A is present in CSF more frequently than it is in blood. HHV-6 has been detected in patients with multiple sclerosis (Virtanen and Jacobson, 2012), and has been associated with epileptic seizures, encephalitis, posttransplant limbic encephalitis, and cognitive dysfunction in hematopoietic stem cell transplant recipients (Michael and Solomon, 2012). HHV-6B and HHV-7 were recently found in association with febrile status epilepticus.

HHV-8 (Kaposi's sarcoma-associated herpesvirus) is found in all forms of Kaposi's sarcoma and is required but not sufficient for the development of the disease. It is also associated with primary effusion lymphoma and multicentric Castleman's disease. HHV-8 DNA has been detected in healthy brains, as well as in some CNS lymphomas and small percentages of specimens from patients with various neurologic disorders (Volpi, 2004).

The only herpesvirus for which approved vaccines exist is VZV. The Varivax varicella vaccine, recommended for children, and the Zostavax zoster vaccine, recommended for adults over 60 years, are live, attenuated vaccines based on the Oka strain of VZV (Gilden, 2011; Gnann, 2012).

Primary and recurrent HSV-1 and HSV-2 infections, zoster, and disseminated infections and encephalitis with these alphaherpesviruses are treatable with the nucleoside analogs acyclovir, valacyclovir, and famcyclovir (McDonald et al., 2012). Antiviral drug therapy is generally not recommended for varicella in immune-competent patients. Virus mutants resistant to these drugs have been reported, typically in immunocompromised patients; phosphonoformate (foscarnet) and cidofovir have been successfully used in such cases. The betaherpesviruses CMV and HHV-6 lack a viral thymidine kinase and are resistant to acyclovir and its derivatives but are sensitive to ganciclovir and its prodrug, valganciclovir (Razonable, 2011). EBV infections generally do not respond well to conventional antivirals.

Polyomaviruses

The first human members of family Polyomaviridae, JC virus (JCV) and BK virus (BKV) (both of genus *Orthopolyomavirus*), were isolated in 1971. Several additional polyomaviruses have been discovered in the recent past, none of which are known to cause neurologic disease. Reactivation of latent JCV in immunecompromised individuals may cause PML (Bellizzi et al., 2012; Ferenczy et al., 2012). Human polyomavirus DNA has also been detected in brain tumors, although the significance of this is uncertain.

Polyomavirus virions are small (~40–50 nm), nonenveloped icosahedral viruses with circular, dsDNA genomes of ~5000 basepairs (bp). JCV attaches to cell surface sialic acid and to the serotonin $5HT_{2A}$ receptor, triggering endocytosis via a clathrin-dependent mechanism (Fig. 2.2, path 1B), followed by trafficking of the virion to the perinuclear space and entry of the genome into the nucleus. Viral genes are transcribed by host RNA polymerase II. The virally encoded large T protein forces the infected cell to enter S phase, during which host DNA synthesis machinery replicates the viral genome. Progeny virions are assembled in the nucleus, but release of virus from the infected cell is not well understood.

Seroprevalence of JCV is >50%. Respiratory transmission is likely. The virus spreads systemically and establishes a chronic, lifelong persistent infection, notably in the kidney, and high levels of virus have been found in urine. Loss of immune competence as a result of HIV infection, lymphoproliferative disease, cancer, or immune-suppressive therapy may allow active replication of JCV in CNS glial cells, resulting in PML. Life expectancy of PML patients is less than 1 year unless the immunodeficiency is corrected. No human polyomavirus vaccines are available, nor are there any approved antiviral drugs for the treatment of polyomavirus infections.

Poxviruses

The poxvirus family (Poxviridae) contains two subfamilies (Chordopoxvirinae and Entomopoxvirinae). Poxviruses that naturally infect humans are chordoxpoxviruses that belong to the *Orthopoxvirus, Molluscipoxvirus*, *Parapoxvirus*, and *Yatapoxvirus* genera. Although best known for producing characteristic skin lesions, with respect to the nervous system, the most significant poxviruses are variola virus (eradicated from the wild), vaccinia virus, and monkeypox virus (all of genus *Orthopoxvirus*), and molluscum contagiosum virus (genus *Molluscipoxvirus*).

Poxvirus virions are large and complex (Fig. 2.1). They can be brick-shaped or ovoid, with lengths of 220–450 nm and widths and thicknesses of 140–260 nm. The virus genome has a condensed nucleoprotein structure in the core. In infectious intracellular mature virions, the core is surrounded by proteinaceous lateral bodies and an envelope containing non-glycosylated virus-encoded membrane proteins. Extracellular enveloped virions have a second envelope. Poxvirus genomes range in length from 135 to 375 kb of linear dsDNA and have hairpin structures at the genomic termini such that, if denatured, the genome becomes a single-stranded circle with a circumference double the genome length. Poxviruses encode ~200 proteins, which are expressed from unspliced transcripts that can be coded on either strand of the genome.

Poxvirus replication takes place in the cytoplasm, which is unusual among DNA viruses, and necessitates the use of a virus-encoded RNA polymerase. Virus entry is via endocytosis (Fig. 2.2, path A2) (Moss, 2012; Schmidt et al., 2012), followed by expression of early genes, some of which play roles in modulating host defenses, while others initiate subsequent steps of replication, which includes genome replication and expression of viral intermediate genes. Intermediate genes enable expression of late genes, whose translation products include virion proteins. Virion assembly takes place in specialized factories that form on cellular membranes near the nucleus. After proteolytic release of spherical immature virions from viral factories, the particles acquire their mature morphology; these virions are released by cell lysis. Some mature virions subsequently acquire a second envelope and are released by an exocytic process (Fig. 2.5, path 6).

Neurologic disease caused by poxvirus infections includes headaches that sometimes accompany the prodromal phase of infection with monkeypox virus and tanapox virus (Damon, 2011), and rare but severe encephalitis following primary vaccination with vaccinia virus (Moss, 2011). The frequency of postvaccination encephalomyelitis (PVEM) is dependent on the vaccinia strain used as the vaccine, with the strain used in the United States (New York Board of Health) being associated with relatively low PVEM incidence. PVEM develops 11–15 days after vaccination in adults and after 6–10 days in infants under 2 years of age, with symptoms consistent with demyelinating encephalomyelitis or direct infection of the CNS. CSF pressure can be elevated but cell counts and chemistry may be normal. Specific diagnosis is difficult, and vaccinia immune globulin has no proven value. The efficacy of newer antivirals (ST-246 and CMX001) is being evaluated; these drugs were used under emergency investigational new drug protocols to treat a patient with progressive vaccinia (Lederman et al., 2012).

Reoviridae

Infections of the murine CNS with mammalian orthoreovirus (family Reoviridae, subfamily Spinareovirinae, genus *Orthoreovirus*) has been extensively used as a model CNS virus pathogenesis system. Rotaviruses (subfamily Sedoreovirinae, genus *Rotavirus*) are a common cause of gastroenteritis, particularly in children. A few case reports link rotavirus infection to CNS complications. Colorado tick fever virus (subfamily Spinareovirinae, genus *Coltivirus*) is a tick-borne virus that can cause headaches, aseptic meningitis, and encephalitis (Romero and Simonsen, 2008).

Reovirus virions are spherical, non-enveloped particles with icosahedral symmetry. The genome consists of multiple segments of double-stranded RNA. Among the best-studied genera are the orthoreoviruses and the rotaviruses. The human orthoreovirus genome consists of 10 segments with a total of approximately 23 000 bp. The human rotavirus genome has 11 segments with a total of approximately 19 000 bp (Taniguchi and Komoto, 2012). Reovirus virions bind to cell surface sialic acid, but additional interaction with cell surface receptors is thought to be necessary for infection (Danthi et al., 2010). Replication occurs in the cytoplasm. After entry, partial uncoating occurs, allowing the virion-associated RNA polymerase to transcribe the genome (McDonald et al., 2009). Positive-sense transcripts act as both mRNAs and as templates for negative-strand synthesis, which occurs during assembly of progeny virions (Trask et al., 2012). Release occurs by lysis but is inefficient (Fig. 2.5, path C1).

There are two Food and Drug Administration-approved, live, attenuated rotavirus vaccines: Rotarix and RotaTeq (Patel et al., 2012). No antiviral drugs are available for the treatment of reovirus infections. Salicylates should be avoided during Colorado tick fever because of possible bleeding disorders.

RNA viruses

Positive-strand RNA viruses (Baltimore class IV)

Picornaviruses

The major genera of family Picornaviridae (order Picornavirales) that include viruses of humans are *Enterovirus, Hepatovirus,* and *Parechovirus*. The human enteroviruses include poliovirus types 1–3 (formally, the *Human enterovirus C* species), coxsackieviruses, echoviruses, and rhinoviruses. Neurologic diseases include the flaccid paralysis of polio, aseptic meningitis, and encephalitis (Rhoades et al., 2011).

Picornavirus virions are non-enveloped icosahedral capsids 28–30 nm in diameter (Fig. 2.1). The genome consists of an infectious linear, 7.2–8.4 kb ssRNA. Infection is initiated by attachment to specific plasma membrane receptors, with subsequent release of viral RNA into the cytoplasm where virus replication takes place (Fig. 2.2, path 1A) (Lin et al., 2009; Daijogo and Semler, 2011; Ogram and Flanegan, 2011; Thibaut et al., 2012). Picornavirus translation is cap-independent and uses an internal ribosomal entry sequence. The translated large precursor polyprotein is self-cleaved into both structural and nonstructural polypeptides. After assembly in the cytoplasm, the mature virus particles are released by cell lysis (Fig. 2.5, path C1).

Typically transmitted by the fecal–oral route, most enteroviral infections are either asymptomatic or subclinical. However, the disease spectrum can range from undifferentiated febrile illness, often accompanied by upper respiratory tract symptoms, to potentially fatal neurologic outcomes. Aseptic meningitis is associated with many coxsackievirus group A and B serotypes, echoviruses, and the polioviruses. Encephalitis and sporadic paralysis are most commonly associated with coxsackieviruses A5–7 (not encephalitis for A5 and A6), A9, and B1–5, echoviruses 6 and 9, and enterovirus 71. The polioviruses are classically associated with flaccid motor paralysis. Chronic meningoencephalitis caused by echoviruses and some coxsackieviruses has been reported in patients with defects in B-lymphocyte function. Viruses of the newly identified *Parechovirus* genus have been associated with aseptic meningitis, meningoencephalitis, and neonatal encephalitis with white-matter injury (Romero and Selvarangan, 2011).

Although no antivirals are available for picornaviruses, live and attenuated vaccines have brought control of polio to near eradication (Pliaka et al., 2012).

Flaviviruses

Members of family Flaviviridae are important causes of encephalitis worldwide (Pierson and Diamond, 2012). The flavivirus transmission cycle involves an amplifying vertebrate reservoir (e.g., birds for West Nile virus (WNV)) and an insect vector (e.g., ticks and mosquitos). Humans typically acquire infection through the bite of an infected mosquito or tick and are usually dead-end hosts. The major human pathogens among the more than 70 members of the *Flavivirus* genus include yellow fever virus, Dengue virus, Japanese encephalitis virus (JEV), St. Louis encephalitis virus (SLEV), Murray Valley encephalitis virus, tick-borne encephalitis virus (TBEV), and WNV (Hollidge et al., 2010; Sips et al., 2012; Turtle et al., 2012). Hepatitis C virus (genus *Hepacivirus*) is an important cause of chronic hepatitis and cirrhosis (Poenisch and Bartenschlager, 2010).

Flavivirus virions are 40–60 nm in diameter and consist of an icosahedral nucleocapsid surrounded by a lipid envelope containing two transmembrane proteins, the membrane protein M and the envelope glycoprotein E. The virus genome is a linear non-segmented ssRNA of ~10 kb that encodes three structural and seven non-structural proteins. Following cell entry via receptor-mediated endocytosis (Fig. 2.2, path A2), virus replication occurs in the host cytoplasm (Kaufmann and Rossmann, 2011; Smit et al., 2011). The precursor polyprotein produced during translation of the genomic RNA is cleaved by viral and host proteases to generate the 10 viral proteins. Assembly of immature, non-infectious virions occurs in association with the endoplasmic reticulum (Pierson and Diamond, 2012). Infectious particles are released by exocytosis after virion budding into the trans-Golgi network (Fig. 2.5, path A/C3).

The neuroinvasiveness of flaviviruses depends on the ability of the virus to enter the CNS, either by penetration of the blood–brain barrier or via axonal transport (Sips et al., 2012; Turtle et al., 2012). Individual viruses have unique predilections for certain areas of the brain. JEV primarily affects developing neurons in thalamus, hippocampus, and midbrain, while anterior horn cells of the spinal cord and brainstem are the primary targets of TBEV.

The majority of JEV infections, the leading cause of viral encephalitis in Asia, are asymptomatic. The disease spectrum of JEV ranges from non-specific febrile illness to aseptic meningitis, meningoencephalitis, flaccid paralysis, and encephalitis (Michael and Solomon, 2012). Parkinsonian movement disorder and seizures have also been reported. Clinical syndromes associated with WNV include meningitis, encephalitis, and acute flaccid paralysis. Neuromuscular weakness, which can occur in up to 50% of patients, distinguishes WNV encephalitis from encephalitis caused by other arboviruses (Ulbert, 2011; Colpitts et al., 2012). SLEV causes three syndromes: febrile headache, aseptic meningitis, and encephalitis. Encephalitis and fatalities are more common in adults, especially in the elderly. TBEV, the most common cause of arboviral encephalitis in Europe, can present with meningitis, meningoencephalitis, poliomyelitis-like flaccid paralysis, and polyradiculoneuritis.

The mosquito-borne dengue virus causes dengue fever, which is typically manifest by fever, headache, musculoskeletal pain, and rash; neurologic manifestations include meningitis, meningoencephalitis, polyneuritis, and parkinsonian symptoms. The risk of neurologic disease is higher in the young and those infected with serotypes 2 and 3.

Hepatitis C virus can cause peripheral neuropathy.

Vaccines for prevention of JEV are available and are used predominantly in Asia. Treatment of hepatitis C virus infections varies depending on the virus genotype, and can include combinations of pegylated interferon-α, ribavirin, boceprevir, or telaprevir (Razonable, 2011). Effective vaccines are not available for most flaviviruses and treatment of infections is supportive (Heinz and Stiasny, 2012).

Togaviruses

Family Togaviridae contains two genera: *Alphavirus* (Gould et al., 2010) and *Rubivirus*. Like flaviviruses, alphaviruses have amplifying vertebrate reservoirs and are primarily transmitted by insect vectors. Togavirus virions are 40–70 nm in diameter, enveloped, and the virus genome is enclosed within an icosahedral capsid (Jose et al., 2009a, b). The envelope has two glycoproteins, E1 and E2, embedded in a host-derived lipid bilayer. E2 is mainly responsible for host cell receptor engagement. The 11–12 kb ssRNA + genome has two protein-coding ORFs.

After attachment, the virion enters the cell by endocytosis (Fig. 2.2, path A2) (Sanchez-San et al., 2009; Wengler, 2009), and then replicates in the cytoplasm (Jose et al., 2009b). Initial translation of the 5' terminal ORF results in a precursor polyprotein which is cleaved to form four non-structural proteins. Synthesis of negative-strand RNA occurs early in infection and is initiated by partially cleaved products of the non-structural polyprotein. Positive-strand RNA and subgenomic mRNAs are subsequently produced using negative-strand antigenomes as the template. The subgenomic mRNA, which corresponds to the 3' third of the genome, is translated to structural proteins. Viral glycoproteins are translated at the endoplasmic reticulum and then

transported to the plasma membrane via the trans-Golgi network. Capsids form in the cytoplasm, and then acquire their envelope as they bud from the plasma membrane (Fig. 2.5, path A/C3) (Jose et al., 2009b; Sanchez-San et al., 2009; Ilkow et al., 2010).

Alphaviruses of clinical importance include Eastern equine encephalitis (EEE), Western equine encephalitis (WEE), and Venezuelan equine encephalitis (VEE) virus, and primarily cause encephalitis (Hollidge et al., 2010; Zacks and Paessler, 2010). EEE virus outbreaks are rare, but have a high case fatality rate (50–70%). Although WEE virus infection tends to be asymptomatic or relatively mild in adults, infants and children <1 year old have higher rates of symptomatic disease. The case fatality rate for WEE virus is 3–7%. VEE virus infections normally cause mild febrile illness in humans, but neurologic disease and sequelae occur; the overall case fatality rate is <1%. In addition, chikungunya virus causes febrile illness that is accompanied by rash, myalgia, arthralgia, headache, and in some instances, neurologic diseases, including severe encephalitis meningoencephalitis, and peripheral neuropathies (Arpino et al., 2009; Das et al., 2010).

No effective vaccine against alphaviruses is available for humans, but live attenuated vaccines are routinely used to protect horses.

The sole member of the *Rubivirus* genus is rubella virus, the cause of rubella (German measles). Humans are the only host for rubella virus. In unvaccinated populations, rubella is a common, generally mild, childhood exanthema (White et al., 2012). Primary infection in adults is more likely to involve fever, malaise, lymphadenopathy, upper respiratory symptoms and, in women, joint pain. Of greatest concern is primary rubella infection in women, particularly during the first 12–16 weeks of pregnancy. There is high likelihood of transplacental transmission and development of congenital rubella syndrome (Duszak, 2009). This syndrome gives rise to multiple, severe congenital abnormalities with high frequency. These include cataracts and retinopathies, heart defects, and neurologic deficits, including mental retardation, psychomotor deficits, and deficits in language and speech. The rubella vaccine, now one component of the measles, mumps, and rubella (MMR) vaccine, has greatly reduced the incidence of both primary rubella and congenital rubella syndrome in developed countries. However, the WHO Rubella Fact Sheet reports that over 100 000 cases of congenital rubella syndrome occur each year.

Coronaviruses

Human coronaviruses belong to order Nidovirales, family Coronaviridae, subfamily Coronavirinae, and either genus *Alphacoronavirus* or *Betacoronavirus*. They typically cause transient respiratory or gastrointestinal illness. The rapidly emergent outbreak in 2003–2004 of severe disease caused by the severe acute respiratory syndrome (SARS)-related coronavirus was notable in many ways, including the presence of neurologic manifestations (Weiss and Leibowitz, 2011).

Coronavirus virions are spherical, 120–160 nm in diameter, with an outer envelope bearing 20-nm-long club-shaped projections that collectively resemble a crown or the solar corona. The ssRNA + genome is coiled inside a helical nucleocapsid of 9–11 nm diameter. At 27–32 kb, coronavirus genomes are the largest among RNA viruses. They are non-segmented, 5'capped, and 3' polyadenylated.

Coronaviruses attach to cell surface receptors and then enter the cell by fusion at the plasma membrane or after endocytosis (Fig. 2.2, paths A2 and A1, respectively) (Perlman and Netland, 2009). Replication occurs in the cytoplasm. After uncoating, genome replication possibly occurs on double-membrane vesicles that originate from the endoplasmic reticulum. A virus-specific RdRp is translated, which transcribes the viral genomic RNA to produce a full-length antigenome. New positive-strand RNA and nested set of subgenomic mRNAs are then transcribed from the antigenome template. Each capped and polyadenylated mRNA produces a single polypeptide. Newly synthesized genomic RNA is incorporated into virions that assemble on membranes between the endoplasmic reticulum and Golgi. Mature virions egress by exocytosis after vesicular transport to the cell membrane (Fig. 2.5, path A/C3).

Coronaviruses are transmitted by respiratory aerosols and usually produce mild upper respiratory infections (Weiss and Leibowitz, 2011). They have been suggested as possible etiologic agents of multiple sclerosis. Neurologic manifestations associated with SARS coronavirus infections include axonopathic polyneuropathy, myopathy, and ischemic stroke. No vaccine or antiviral is available for human coronavirus infections.

Negative-strand RNA viruses (Baltimore class V)

Arenaviruses

Rodents are the primary hosts of arenaviruses. Virus transmitted from chronically infected but asymptomatic animals can cause significant disease in humans (Charrel et al., 2011). Some arenaviruses, including Lassa fever virus (family Arenaviridae, genus *Arenavirus*; species, *Lassa virus*) cause hemorrhagic disease that have high case fatality rates. Lymphocytic choriomeningitis virus (family Arenaviridae, genus *Arenavirus*, species *Lymphocytic choriomeningitis virus*) can cause aseptic meningitis (rarely fatal), hydrocephalus, and more severe CNS disease (Bonthius, 2012).

Arenavirus virions are enveloped and range in diameter from 40 to >200 nm. Their granular appearance in electron micrographs is due to the incorporation of ribosomes into the virion interior. Arenavirus genomes consist of two segments of ssRNA–. The L segment is ~7.2 kb and S is ~3.5 kb. Different from most other negative-strand viruses, arenavirus genomes encode proteins on both strands and are thus ambisense. They are considered to be negative-strand viruses because the RdRp is coded on the antigenome L strand and there is no evidence that their genomes can function as mRNAs. The S segment encodes the virion glycoprotein on the genomic strand and the nucleoprotein on the antigenome strand, while the S segment encodes the Z protein on the genomic strand and the RdRp on the antigenome strand.

Many arenaviruses use a widely distributed protein, αDG, as their receptor. After binding and endocytosis (Fig. 2.2, path A2), virion contents are released into the cytoplasm after pH-dependent membrane fusion. The initial round of transcription produces subgenomic length mRNAs for the RdRp and the nucleoprotein. As nucleoprotein levels increase, full-length antigenomes are transcribed, which are initially transcribed to subgenome-length mRNAs that encode the glycoprotein (S segment) and the Z protein (L segment).

Transmission to human mucosa is via contact with rodents or their residues. A 10-day prodrome period characterized by fever, myalgia, and other symptoms usually precedes onset of meningitis, which is accompanied by an increase in CSF mononuclear cell levels. Encephalitis develops in 5–34% of hospitalized patients. Most patients with lymphocytic choriomeningitis virus CNS disease fully recover. Based on studies in mice, CNS infections are controlled by T-cell responses, but those same responses attack infected cells in the leptomeninges and ependyma, leading to breaches in the blood–brain barrier and subsequent disorder and loss of brain function. Human-to-human transmission is rare.

Although ribavirin inhibits arenavirus replication in cell culture, it does not penetrate into the brain and is of no value for CNS disease. No vaccines are available for the prevention of arenavirus infections.

Bunyaviruses

Bunyaviruses are vectored by arthropod bites and transmitted from rodent excreta, and cause diseases that include febrile illness, hemorrhagic fevers, respiratory and pulmonary syndromes, and encephalitis (Walter and Barr, 2011). Examples include hantavirus pulmonary syndrome caused by the sin nombre virus (family Hantaviridae, genus *Hantavirus,* species *Sin nombre virus*), and encephalitis caused by California encephalitis virus and La Crosse virus (both belong to family Hantaviridae, genus *Orthobunyavirus,* species *California encephalitis virus*) (Hollidge et al., 2010). Among the California viruses, La Crosse virus is the most important human pathogen (Hollidge et al., 2010).

Bunyavirus virions are somewhat spherical, with diameters of 80–120 nm (Walter and Barr, 2011; Guu et al., 2012). They consist of three ribonucleocapsids, each built from one of the three genomic segments complexed with the nucleocapsid protein and the viral RdRp, all contained in an envelope that is studded with the two viral glycoproteins. The genome consists of three segments of ssRNA, large (L, 6.4–12.2 kb), medium (M, 3.6–4.9 kb), and small (S, 1–2.9 kb). All bunyaviruses code their structural proteins on the antigenome strand, and are thus considered to be negative-strand viruses. Some bunyaviruses express non-structural genes on their genomic strand, an ambisense coding strategy. For orthobunyaviruses, the S segment encodes the nucleocapsid protein and a non-structural protein, a polyprotein encoded by the M segment, is proteolytically processed to the two glycoproteins and a non-structural protein, and the L segment encodes the RdRp.

Viral glycoproteins mediate cell surface receptor binding that triggers endocytosis followed by low-pH-dependent membrane fusion that releases virion contents into the cytoplasm (Fig. 2.2, path A2). Primary transcription by the virion-associated RdRp produces mRNAs for translation of the structural genes, as well as production of full-length antigenomes that serve as templates for transcription of ambigene mRNAs and new virus genomes. Maturational processing and transport of the viral glycoproteins lead to their accumulation on Golgi membranes and the plasma membrane, where they associate with viral nucleoprotein complexes. Enveloped virions form by budding either into the Golgi, from which they are transported to the cell surface for exocytic release (Fig. 2.5, path A/C3), or from the plasma membrane, resulting in direct release (Fig. 2.5, path A/C2).

After transcutaneous injection from an infected mosquito, California encephalitis virus and its close relatives spread to and then replicate in skeletal muscle. Secondary transmission by plasma viremia results in infection of other tissues, including the neurons and glial cells of the cerebral cortex and brainstem. Infection results in a variety of pathologic features, including cerebral edema, perivascular cuffing, and focal necrosis typical of encephalitis. Typical cases can include initial rapid onset of transient (3–7 days) symptoms – fever, stiff neck, lethargy, and vomiting. More severe cases include seizures and coma. Most patients recover completely, but some experience epilepsy, and persistent paresis.

Antivirals are not available. Some inactivated virion vaccines are in limited use.

Orthomyxoviruses

Influenza viruses A, B, and C (family Orthomyxoviridae, genera *Influenzavirus A, Influenzavirus B*, and *Influenzavirus C*) are well known as the causes of influenza. Complications of influenza that affect the nervous system include encephalopathy, encephalitis, and Reye's syndrome (associated with influenza B) (Kuiken et al., 2012).

In fresh isolates, influenza virus virions are often filamentous rods >300 nm long, while laboratory strains are often 100-nm-diameter spheres (Imai and Kawaoka, 2012). Virion cores consist of eight (influenza viruses A and B) or seven (influenza virus C) segments of the genomic ssRNA– , complexed with the nucleoprotein and the three subunit RdRp. These ribonucleoprotein complexes are surrounded by an envelope coated on its inner surface by a layer of matrix protein. Influenza A and B virion envelopes are studded with viral hemagglutinin (HA) and neuraminidase (NA) glycoproteins. Influenza C virion envelopes contain a single glycoprotein, HEF. The envelopes of all three viruses also contain a small transmembrane protein with ion channel activity. The genomic segments range in length from ~0.9 to ~2.4 kb, with a summed genome length of ~14 kb. Most of the genome segments encode a single protein, but in each of the influenza viruses, two or three genome segments produce multiple proteins by RNA splicing, alternative initiation codons, or polyprotein cleavage.

Cell entry is mediated by HA (or HEF) binding to sialic acids on cell surface proteins, which triggers endocytosis (Fig. 2.2, path A2) (Imai and Kawaoka, 2012). Vesicle acidification leads to a major conformational change in HA (or HEF) that unleashes its membrane fusion activity, resulting in fusion of the virion envelope with the vesicle membrane. Vesicle acidification also results in diffusion of protons through the virion envelope ion channel, acidifying the virion interior, an essential step in uncoating. After fusion and uncoating, the virion ribonucleoprotein is transported to the nucleus, where the initial round of mRNA transcription and genome replication takes place. After translation in the cytoplasm, membrane-associated proteins mature, and are then transported to the plasma membrane; nucleoproteins and RNA polymerase subunits are transported to the nucleus. Viral ribonucleoprotein complexes destined for incorporation into new virions form in the nucleus and are transported through nuclear pores and then to the plasma membrane, where they associate with the membrane proteins and bud to form infectious virions (Fig. 2.5, path 1A/2B/C2) (Rossman and Lamb, 2011). The NA (or HEF esterase activity) protein is needed to remove cell surface sialic acids so nascent virions are not retained at the cell surface by interaction with these virus receptors.

An important aspect of influenza A virus biology is the existence of multiple antigenically distinct forms of the HA and NA glycoproteins (Reperant et al., 2012). Sixteen major antigenic types of HA (HA1 through HA16) have been identified as well as nine types of NA (NA1 through NA9). Only a limited number of these (HA1, HA2, and HA3, as well as NA1 and NA2) are found in human influenza A viruses, although all are found in animal influenza viruses. Although humans are generally not good hosts for animal influenza A viruses, certain species, e.g., pigs, can be infected with human and animal influenza A viruses. Coinfection with multiple influenza viruses can, through genetic reassortment of genome segments, give rise to novel viruses able to replicate in humans and having HA and/or NA glycoproteins against which there is little or no pre-existing immunity in the human population. This is known as antigenic shift. Such reassortant viruses can give rise to influenza pandemics, as occurred in 2009. A pandemic might also result if an animal influenza A virus, such as a highly pathogenic avian influenza A virus, adapted to human hosts directly by mutation. The currently circulating human influenza A viruses continuously change the antigenicity of their HA and NA glycoproteins by mutation, a phenomenon known as antigenic drift. This necessitates annual modification of the influenza vaccine. Antigenic variants of influenza B and C viruses are known but these viruses have little or no pandemic potential.

Transmission of influenza viruses occurs by inhalation of respiratory aerosols. The virus replicates in superficial cells of the upper and lower respiratory tract, as well as lung-associated macrophages and dendritic cells. In uncomplicated influenza, a short incubation period (1–5 days) is typically followed by a disease course that includes chills, headache, and dry cough, followed by fever, myalgia, and other symptoms that persist for 3–8 days (longer in the elderly). More severe cases result from replication of the virus in the lower respiratory tract and lungs (pneumonia). Replication of human influenza A virus outside the respiratory tract appears to be limited. This is due to requirement for cleavage of HA by tryptase Clara, which is secreted by Clara cells in the ciliated epithelium of the airway. However, highly pathogenic avian influenza A viruses contain polybasic HA cleavage sites, enabling cleavage by more widely expressed proteases, allowing these viruses to spread systemically. Despite having limited ability to replicate outside the respiratory tract, the neurologic complications of human influenza virus infections include encephalopathy (Reye's syndrome and acute necrotizing encephalopathy), encephalitis, stroke, and myelitis. Although reported in association with a swine influenza vaccination program in the 1970s, the incidence of

Guillain–Barré syndrome is not elevated in association with influenza epidemics.

Inactivated and live attenuated vaccines are available for prevention of influenza caused by circulating strains of influenza A and B viruses (Osterholm et al., 2012). Current multivalent vaccines contain an H1N1 influenza A strain, an H3N2 influenza A strain, and an influenza B strain. The strains included in the vaccines are based on annual recommendations by the World Health Organization.

Influenza A and B infections are treatable with the antiviral drugs oseltamivir (Tamiflu) and zanamivir (Relenza), which target the viral neuraminidase (Razonable, 2011). Oseltamivir may be taken orally and is more frequently prescribed than zanamivir, which must be inhaled. However, resistance to oseltamivir appears to develop more readily than to zanamivir. Amantidine and rimantidine are older drugs that inhibit the ion channel of influenza A viruses. Due to limited effectiveness, widespread resistance, side-effects, and the availability of neuraminidase inhibitors, these drugs are seldom used.

Paramyxoviruses

The human paramyxoviruses of greatest relevance here are measles virus (order Mononegovirales, family Paramyxoviridae, genus *Morbillivirus*) and mumps virus (order Mononegovirales, family Paramyxoviridae, genus *Rubulavirus*). Measles virus can cause encephalitis and subacute sclerosing panencephalitis, and mumps virus can cause encephalitis and transverse myelitis (Hviid et al., 2008; Buchanan and Bonthius, 2012).

Paramyxovirus virions are most often spherical and >150 nm in diameter (Rima and Duprex, 2009). The genome and nucleocapsid proteins (one of which is the viral RdRp) form a flexible helical complex 13–18 nm in diameter. The nucleocapsid is contained in an envelope that contains the viral fusion protein and a hemagglutinin-neuraminidase (no neuraminidase activity for measles virus). The ssRNA– genomes are 15–19 kb long and encode 7–11 protein genes, most of which are expressed from independent capped and polyadenylated transcripts. Paramyxovirus fusion (F) proteins have the unusual ability to trigger membrane fusion at neutral pH.

Paramyxoviruses enter cells by fusion at the plasma membrane and perform all of their replicative activities in the cytoplasm (Fig. 2.2, path A1) (Chang and Dutch, 2012). mRNA transcription is initiated at a single promoter, with each gene being transcribed sequentially as the viral RNA polymerase proceeds along the genome, pausing at the end of each transcribed gene to release the transcript and then begin transcription of the next gene. Paramyxovirus virions are enveloped by budding at the plasma membrane (Fig. 2.5, path A/C2) or intracellular membranes that contain virion envelope proteins (Fig. 2.5, path A/C3) (Harrison et al., 2010).

Measles and mumps viruses infect epithelial cells of the respiratory tract and then spread by viremia in lymphocytes (de Vries et al., 2012). Secondary replication of measles virus occurs in lymphoid and endothelial cells and can involve many tissues. Clinical symptoms proceed from fever, to cough and conjunctivitis, and then to Koplik's spots on the oral mucosa and a generalized rash that persists for about a week. Beginning at rash onset, T-cell and monocyte responses are markedly suppressed for several weeks, leading to susceptibility to other infections. Cellular immunity is essential for recovery from measles (Griffin et al., 2012). Although antibodies can contribute to recovery from measles, they are not essential. Measles virus infections can lead to three neurologic diseases. Acute disseminated encephalomyelitis is a transient autoimmune demyelinating disease that occurs about a week after the rash phase in 0.1% of cases. Measles inclusion body encephalitis is a rare progressive disease that occurs predominantly in immune-suppressed individuals. Subacute sclerosing panencephalitis occurs in 1 of 10^4–10^5 cases and involves a persistent infection of the brain that can progress for years (Tatli et al., 2012).

Secondary infection of mumps virus takes place in a wide variety of tissues, including parotid glands, testes, endothelial cells, and the CNS (Hviid et al., 2008). As evidenced by pleocytosis, about half of mumps cases involve CNS infections, with meningitis in <15%, and encephalitis in <1%. Aseptic meningitis is the most common neurologic manifestation of mumps virus infection. Transmissible virus is present in saliva for about 1 week, and in urine for several weeks. Neutralizing antibodies are important for controlling mumps, but cellular immunity also plays a role.

Highly effective live attenuated vaccines for measles and mumps have been in widespread successful use since the 1960s, but these viruses remain important internationally, and outbreaks still occur when vaccine coverage is incomplete or virus is imported from endemic regions (Demicheli et al., 2012; White et al., 2012).

Rhabdoviruses

Rabies virus (order Mononegovirales, family Rhabdoviridae, genus *Lyssavirus*) causes rabies, which, when untreated, essentially invariably causes an acute progressive, and ultimately fatal, encephalitis (Nigg and Walker, 2009; Yousaf et al., 2012). Rabies virus virions are cylindrical (~180 nm long and ~80 nm in diameter), with one rounded and one flat end, and have the appearance of a bullet (Fig. 2.1). Virions are helical in form, consisting of

the nucleocapsid-coated virus genome and its associated RdRp, surrounded by the matrix protein and wrapped in an envelope that is studded with 300–400 copies of the viral glycoprotein. The genome is a single 11.9-kb segment of ssRNA that encodes five genes.

Endocytic virus entry is mediated by interaction of the glycoprotein with a cellular receptor (Fig. 2.2, path A2). After low pH-dependent membrane fusion, the ribonucleoprotein core is delivered into the cytoplasm, where replication occurs. Primary transcription by the virion-associated RdRp results in sequential production of five capped and polyadenylated monocistronic mRNAs (one for each viral protein) (Albertini et al., 2011). Subsequent rounds of replicative transcription produce the full-length antigenome and then new negative-strand genomes. Nucleocapsid-coated genomes and the matrix protein unite with glycoprotein-rich membrane domains to form virions that bud from the cell surface (Fig. 2.5, path A/C2) (Okumura and Harty, 2011).

Most often transmitted through skin by animal bites (Briggs, 2012), the virus is transmitted directly to peripheral neurons and then to the brain, or neuronal transmission occurs after amplification in skeletal muscles. Disseminated infection, including transmission from the brain to salivary glands, occurs late in disease.

Rabies testing should be done for all cases of acute progressive encephalitis of unknown etiology. Bite wounds should be disinfected immediately to reduce virus inoculum (Jackson, 2011). As an adjunct to postexposure administration of rabies vaccine (Briggs, 2012; Warrell, 2012), rabies immunoglobulin (from hyperimmunized humans) is recommended to be injected at the site of injury (reduces virus load and spread) (Nigg and Walker, 2009; Jackson, 2011).

Reverse transcribing viruses (Baltimore class VI)

Retroviruses

The major human retroviruses include human T lymphotropic viruses 1 and 2 (HTLV-1 and -2; family Retroviridae, genus *Deltaretrovirus*) and HIV-1 and -2) (family Retroviridae, genus *Lentivirus*). Retrovirus virions are enveloped, 80–100 nm in diameter, and contain an outer matrix and an inner capsid that contains the virus genome (Fig. 2.1) (Ganser-Pornillos et al., 2012). The envelope consists of a lipid bilayer and glycoproteins. The icosahedral capsid is built of the gag protein. Retrovirus virions are diploid, containing two identical copies of the genome, which is linear, ssRNA+, and 7–11 kb long. Retroviruses are unique in their ability to retrotranscribe their RNA genomes into dsDNA with the help of their RNA-dependent DNA polymerase, reverse transcriptase (Le Grice, 2012). In contrast to the "simple" retroviruses (e.g., avian leucosis virus) that encode only the viral gag, pol, and env proteins, HTLVs and HIVs are "complex" retroviruses that encode additional accessory genes.

Retrovirus replication begins with virion binding to host cell surface receptors via surface glycoproteins (Klasse, 2012; Wilen et al., 2012). Conformational change in env proteins results in fusion of viral and cellular membranes (Fig. 2.2, path A1). After entry into host cell, viral DNA is retrotranscribed in the cytoplasm and the nascent viral DNA is transported to the host nucleus, where the virally encoded integrase enzyme mediates its incorporation into random sites in the host genome (Krishnan and Engelman, 2012). The integrated provirus genome acts as a template for transcription of viral RNA by cellular RNA polymerase II. Splicing of some transcripts produces subgenomic mRNAs that are translated to produce viral proteins. Virion assembly begins in the cytoplasm, with virions acquiring their envelope and emerging from the infected cell by budding from plasma membrane (Fig. 2.5, path 1A/2B/C2) (Ganser-Pornillos et al., 2012; Lee et al., 2012).

The major routes of transmission for the important human retroviruses include sexual transmission, parenteral transmission, and from mother to child. HTLV-1 has been associated with adult T-cell leukemia/lymphoma, infective dermatitis, and, rarely, polymyositis (Cook et al., 2013). Both HTLV-1 and HTLV-2 have been associated with HTLV-associated myelopathy/ tropical spastic paraparesis, a chronic progressive demyelinating disease that affects the spinal cord and white matter of the CNS. HIV-associated neurologic disorders include neurocognitive disorders and peripheral neuropathies as well as vacuolar myelopathy (Mirza and Rathore, 2012; Spudich and Ances, 2012). HIV-associated neurocognitive disorder includes HIV-associated dementia, mild neurocognitive disorder, and asymptomatic neurocognitive impairment. Other primary neurologic syndromes associated with HIV include aseptic meningitis, multiple sclerosis-like disorders, ischemic and hemorrhagic strokes, primary HIV-induced headache and psychiatric disorders.

The advent of highly active antiretroviral drugs that target almost every step in the HIV replication cycle has revolutionized the treatment of HIV (Tan and McArthur, 2012). No vaccines are approved for the prevention of HIV infection.

FUNDAMENTAL ASPECTS OF VIRAL PATHOGENESIS

Viral pathogenesis involves several steps that must occur for the virus to infect and cause disease in the host: virus entry into the host, primary virus replication, virus spread within the host, infection of cells with special affinities for the virus (cell tropism), cellular injury, host

immune response, viral clearance or persistence, and viral shedding and transmission.

Virus entry occurs either through the mucosa of the respiratory, gastrointestinal tract, or urogenital tract, by transcutaneous inoculation into the blood stream through blood transfusion or insect vector bites, and by maternal–fetal transmission across the placenta. Virus replication usually occurs at the portal of entry and can cause disease there; for example, influenza virus and respiratory disease, and rotaviruses and gastrointestinal disease. Some viruses produce diseases at sites distant from their portal of entry. The mechanism of spread varies; viruses may reach their target cells via nerves or through the blood stream or lymphatics. Viruses also have affinity for certain organ and cell types. Such cell tropism is usually mediated by specific cell surface receptors on the host cell with which the virus envelope or capsid can interact to initiate infection. Viruses produce cellular injury by either direct destruction of the infected cell or by alteration in cell physiology. Inactivation of host cellular protein synthesis is a hallmark of many virus infections. Cellular damage may ultimately result in clinical illness, though this depends on several factors, including the host immune response to viral infection.

Some viruses can persist in the host for a prolonged period of time. In chronic infections, the virus can be continuously detected in the host (e.g., infections with hepatitis viruses B or C). During virus latency, the virus persists in a dormant (non-replicating) form, but can reactivate intermittently to an infectious form (e.g., HSV-1 and HSV-2).

IMMUNITY TO VIRUSES

The host immune response to viral infection is a complex process involving both innate and adaptive immunity. In immune-competent individuals, most virus infections are self-limiting and recovery is associated with clearance (elimination) of the virus. The innate immune response is a local, antigen-independent defense mechanism that detects unique structural molecules present in microbes called pathogen-associated molecular patterns (PAMPs). PAMPs are recognized by membrane-associated or cytosolic pattern recognition receptors (PRRs) present in most body defense cells. Viral PAMPs like DNA, ssRNA, and dsRNA are recognized by three classes of PRPs: the Toll-like receptors, retinoic acid-inducible gene-like receptors, and nucleotide oligomerization domain-like receptors (Takeuchi and Akira, 2009). Recognition of viral nucleic acids by PRRs activates signaling pathways, resulting in production of type 1 interferons (IFNs). Further upregulation of IFN-induced gene products helps in the suppression of viral replication and confers resistance to infection for uninfected cells. IFNs and other cytokines play a role in bridging innate and adaptive antiviral immune response.

Adaptive or acquired immunity is an antigen-specific immune response and consists of T-cell-mediated cellular and virus-specific antibody-mediated humoral immunity. Cellular immunity is primarily mediated by CD8+ cytotoxic T lymphocytes, which lyse virus-infected cells with perforins and granzymes after presentation of virus antigens by MHC class I proteins. Virus-derived MHC class II-associated oligopeptides activate CD4+ T cells, which mainly act as T helper cells expressing cytokines, although they can also display cytolytic activity. Humoral immunity helps protect against initial viral infection in vaccinated hosts or reinfections in previously infected patients. Neutralizing IgA protects against viruses that enter through mucosal surfaces, while IgM and IgG provide protection against blood-borne viruses.

Viruses employ a plethora of strategies to outwit the immune system and evade detection and destruction. The strategies vary depending on individual viruses and include evasion of cytotoxic T lymphocytes and natural killer cells and modulating MHC function, interference with interferons, inhibition of humoral responses, inhibition and modulation of cytokines and chemokines, regulation of apoptosis, and inhibition of inflammation.

DIAGNOSIS OF VIRAL INFECTIONS

Laboratory tools for diagnosis of suspected viral infections are not always available, nor is their use always economically or clinically justified. Laboratory diagnosis of suspected viral infections can involve a wide array of methods, including detection of the agent by growing it in cell culture, visualizing it directly in the specimen by electron microscopy, detection of virus antigens in body fluids or tissues, and detection of viral nucleic acids. Immunologic responses to viruses can be detected by serologic procedures that detect virus-specific antibodies or by responses of T cells to virus antigens (see Chapter 5).

Detection of virus infections of the CNS poses a special challenge, as viral burden in CSF may be low. Serologic procedures to detect IgM in CSF are routinely employed to diagnose neurotropic arboviral infections. However, the diagnosis of CNS viral infections has been revolutionized by nucleic acid amplification that greatly reduces the need to perform open-brain biopsies for diagnostic purposes.

ANTIVIRALS

Our understanding of the critical steps in virus replication cycles has contributed to the identification of numerous potential targets for antiviral therapy. Currently available antivirals target viral replication enzymes, proteases, and entry and exit pathways. Entry of HIV into host cell can be blocked by enfuvirtide (which binds to gp41 on the surface

of HIV virion) and maraviroc (which blocks binding of HIV to CCR-5). Amantadine and rimantadine inhibit uncoating of influenza A virus by inhibiting the ion channel function of the membrane protein M_2. A number of antivirals inhibit nucleic acid synthesis, targeting viral DNA and RNA polymerases. Inhibition of HIV reverse transcriptase can be achieved by both nucleoside (e.g., zidovudine) and non-nucleoside (e.g., efavirenz) inhibitors. Drugs that inhibit viral proteases are currently in clinical practice against HIV (e.g., atazanavir) and hepatitis C virus (e.g., telaprevir). Specific inhibitors of enzymes necessary for hepatitis C virus replication are currently under development. In addition to the NS3/4A serine protease inhibitors (e.g., boceprevir), studies with NS5B RNA-dependent RNA polymerase inhibitors (e.g., filibuvir), NS5A inhibitors (e.g., BMS-790052), and cyclophilin inhibitors (e.g., alisporivir) are currently under way. Oseltamivir and zanamavir are potent inhibitors of neuraminidase, the enzyme required for release of newly formed influenza virions from infected cells.

The mechanisms of action of some therapeutic agents employed against viruses are not specific. As part of the host innate immune response, interferon-α inhibits a broad spectrum of viruses, as detailed earlier, and is routinely used in the treatment of hepatitis B virus and hepatitis C virus infection. Ribavarin is a competitive inhibitor of the cellular enzyme inosine monophosphate dehydrogenase. The resultant decrease in intracellular guanosine triphosphate leads to inhibition of viral nucleic acid and protein synthesis. Better understanding of virus replication cycles will enable development of novel antiviral therapies against existing and emerging pathogens (De Clercq, 2013).

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