can be efficiently transcribed or translated; (3) proteins that promote cell survival or inhibit apoptosis so that progeny virus can mature and escape from the infected cell; (4) proteins that inhibit the host interferon response; and (5) proteins that downregulate host inflammatory or immune responses so that viral infection can proceed in an infected person to the extent consistent with the survival of the virus and its efficient transmission to a new host. More complex viruses of the poxvirus or herpesvirus family encode many proteins that serve these functions. Some of these viral proteins have motifs similar to those of cellular proteins, while others are quite novel. Virology has increasingly focused on these more sophisticated strategies evolved by viruses to permit the establishment of long-term infection in humans and other animals. These strategies often provide unique insights into the control of cell growth, cell survival, macromolecular synthesis, proteolytic processing, immune or inflammatory suppression, immune resistance, cytokine mimicry, or cytokine blockade.

*MicroRNAs* (miRNAs) are small noncoding RNAs that can regulate gene expression at the posttranscriptional level by targeting—and usually silencing—mRNAs. miRNAs were initially discovered in plants and plant viruses, where they alter expression of cell defensins. Herpesviruses are especially rich in miRNAs; for example, at least 23 miRNAs have been identified in EBV and 11 in CMV. Adenovirus and polyomavirus miRNAs have also been described. Increasing data indicate that animal viruses encode miRNAs to alter the growth and survival of host cells and the innate and acquired immune responses.

### HOST RANGE

The concept of host range was originally based on the cell types in which a virus replicates in tissue culture. For the most part, the host range is limited by specific cell-surface proteins required for viral adsorption or penetration—i.e., to the cell types that express receptors or co-receptors for a specific virus. Another common basis for host-range limitation is the degree of transcriptional activity from viral promoters in different cell types. Most DNA viruses depend not only on cellular RNA polymerase II and the basal components of the cellular transcription complex but also on activated components and transcriptional accessory factors, both of which differ among differentiated tissues, among cells at various phases of the cell cycle, and between resting and cycling cells.

The importance of host range factors is illustrated by the effects of specific host determinants that limit the replication of influenza virus with avian or porcine hemagglutinins in humans. These viral proteins have adapted to bind avian or porcine sialic acids, and spread of avian or porcine influenza viruses in human populations is limited by their ability to infect human cells.

### VIRAL CYTOPATHIC EFFECTS AND INHIBITORS OF APOPTOSIS

The replication of almost all viruses has adverse effects on the infected cell, inhibiting cellular synthesis of DNA, RNA, or proteins through efficient competition for key substrates and enzymatic processes. These general inhibitory effects enable viruses to nonspecifically limit components of innate host resistance, such as interferon (IFN) production. Viruses can specifically inhibit host protein synthesis by attacking a component of the translational initiation complex—frequently, a component that is not required for efficient translation of viral RNAs. Poliovirus protease 2A, for example, cleaves a cellular component of the complex that ordinarily facilitates translation of cellular mRNAs by interacting with their cap structure. Poliovirus RNA is efficiently translated without a cap because it has an internal ribosome entry sequence. Influenza virus inhibits the processing of mRNA by snatching cap structures from nascent cellular RNAs and using them as primers in the synthesis of viral mRNA. HSV has a virion tegument protein that inhibits cellular mRNA translation.

Apoptosis is the expected consequence of virus-induced inhibition of cellular macromolecular synthesis and viral nucleic acid replication. Although the induction of apoptosis may be important for the release of some viruses (particularly nonenveloped viruses), many viruses have acquired genes or parts of genes that enable them to forestall infected-cell death. This delay increases the yield from viral replication. Adenoviruses and herpesviruses encode analogues of the cellular Bc12 protein, which block mitochondrial enhancement of proapoptotic stimuli. Poxviruses and some herpesviruses also encode caspase inhibitors. Many viruses, including HPVs and adenoviruses, encode proteins that inhibit p53 or its downstream proapoptotic effects.

## VIRAL INFECTION IN VIVO

### TRANSMISSION

The capsid and envelope of a virus protect the genome and enable efficient transmission of the virus from cell to cell and to new prospective hosts. Most common viral infections are spread by direct contact, by ingestion of contaminated water or food, or by inhalation of aerosolized particles. In all these situations, infection begins on an epithelial or mucosal surface and spreads along the mucosa and into deeper tissues. Infection may spread to cells that can enter blood vessels, lymphatics, or neural circuits. HBV, HCV, HTLV, and HIV are dependent on transmission by parenteral inoculation. Some viruses are transmitted only between humans. The dependence of smallpox virus and poliovirus infections on interhuman transmission makes it feasible to eliminate these viruses from human circulation by mass vaccination. Herpesviruses also survive by interhuman transmission but may be more difficult to eliminate because they establish persistent latent infection in humans and continuously reactivate to infect new and naïve generations.

Animals are also important reservoirs and vectors for transmission of viruses causing human disease. Insect vectors can mediate parenteral transfer of viruses that reach high titers in animal or human hosts. Arboviruses are parenterally transmitted from mammalian species to humans by mosquito vectors. Herpes B, monkeypox, rabies, and viral hemorrhagic fevers are other examples of zoonotic infections caused by direct contact with animals, animal tissues, or arthropod vectors.

### PRIMARY INFECTION

Initial viral infections usually last for several days or weeks. During this period, the concentration of virus at sites of infection rises and then falls, usually to unmeasurable levels. The rise and fall of viral replication at a given site depend on local innate immune responses and the access of systemic antibody and cell immune effectors to the virus. Typically, primary infections with enteroviruses, mumps virus, measles virus, rubella virus, rotavirus, influenza virus, AAV, adenovirus, HSV, and VZV are cleared from almost all sites within 3–4 weeks. Some viruses are especially proficient in altering or evading innate and acquired immune responses. Primary infection with AAV, EBV, or CMV can last for several months. Characteristically, primary infections due to HBV, HCV, hepatitis D virus (HDV), HIV, HPV, and molluscum contagiosum virus (MCV) extend beyond several weeks. For some of these viruses (e.g., HPV, HBV, HCV, HDV, and MCV), the manifestations of primary infection are almost indistinguishable from the persistent phase.

Disease manifestations usually arise as a consequence of viral replication, infected-cell injury or death, and local inflammatory and innate immune responses. Disease severity may not necessarily correlate with the level of viral replication alone. For example, the clinical manifestations of intense primary infection with poliovirus, enterovirus, rabies virus, measles virus, mumps virus, or HSV at mucosal surfaces may be inapparent or relatively mild, whereas limited replication in neural cells can have dramatic consequences. Similarly, rubella virus or CMV infections in utero or neonatal HSV infections may have much more devastating effects than infections in adults.

Primary infections are cleared by nonspecific innate and specific adaptive immune responses. Thereafter, an immunocompetent host is usually immune to the disease manifestations of reinfection by the same virus. Immunity frequently does not prevent transient surface colonization on reexposure, persistent colonization, or even limited deeper infection.