within the terminal inverted repeats, and the inverted repeats self-prime complementary-strand synthesis by the virus-encoded DNA polymerase. Like herpesviruses, poxviruses encode several enzymes that increase deoxynucleotide triphosphate precursor levels and thus facilitate viral DNA synthesis.

VIRUSES THAT USE BOTH RNA AND DNA GENOMES IN THEIR LIFE CYCLE Retroviruses, including HIV, are RNA viruses that use a DNA intermediate to replicate their genomes. In contrast, hepatitis B virus (HBV) is a DNA virus that uses an RNA intermediate to replicate its genome. Thus these viruses are not purely RNA or DNA viruses. Retroviruses are RNA viruses with two identical sense-strand genomes and associated reverse transcriptase and integrase enzymes. Retroviruses differ from all other viruses in that they reverse-transcribe themselves into partially duplicated double-strand DNA copies and then routinely integrate into the host genome as part of their persistence and replication strategies. Inhibitors of reverse transcriptase (e.g., zidovudine) or integrase (e.g., raltegravir) are now commonly used as antiviral treatments for HIV infection. Integration of remnants and even complete copies of simple retrovirus DNAs into the human genome raises the possibility of replication-competent simple human retroviruses. However, endogenous human retrovirus replication has not been documented or associated with any disease. Integrated, replication-competent retroviral DNAs are also present in many animal species, such as pigs. These porcine retroviruses are a potential cause for concern in xenotransplantation because retrovirus replication could cause disease in humans.

Cellular RNA polymerase II and transcription factors regulate transcription from the integrated provirus DNA genome. Some retroviruses also encode regulators of transcription and RNA processing, such as Tax and Rex in human T lymphotropic virus (HTLV) types 1 and 2. HIV-1 and HIV-2 have orthologous Tat and Rev genes as well as the additional accessory proteins Vpr, Vpu, and Vif, which are important for efficient infection and immune escape. Full-length proviral transcripts are made from a promoter in the viral terminal repeat and serve as both genome RNAs that are packaged in the nucleocapsids and differentially spliced mRNAs that encode for the virus Gag protein, polymerase/integrase protein, and envelope glycoprotein. The Gag protein includes a protease that cleaves it into several components, including a viral matrix protein that coats the viral RNA. Viral RNA polymerase/integrase, matrix protein, and cellular tRNAs are key components in the viral nucleocapsid. Protease inhibitors have been developed as effective agents against infections caused by HIV (e.g., saquinavir) or hepatitis C virus (HCV) (e.g., telaprevir).

HBV replication is unique in several respects. The HBV genome is a partially double-strand DNA genome that is repaired in infected cells to a fully double-strand circular DNA by the virion polymerase. Viral mRNAs are transcribed from the closed circular viral episome by the cellular RNA polymerase II and are translated to yield HBV proteins, including core protein, surface antigen, and polymerase. In addition, a full-genome-length mRNA is packaged into viral core particles in the cytoplasm of infected cells as an intermediate for viral DNA replication. This RNA associates with the viral polymerase, which also has reverse transcriptase activity and converts the full-length encapsidated RNA genome into partially double-strand DNA. Thus, nucleos(t)ide analogs that inhibit reverse transcription (e.g., tenofovir) are commonly used to treat HBV infection. HBV is believed to mature by budding through the cell's plasma membrane, which has been modified by the insertion of viral surface antigen protein.

Viral Assembly and Egress For most viruses, nucleic acid and structural protein synthesis is accompanied by the assembly of protein and nucleic acid complexes. The assembly and egress of mature infectious virus mark the end of the *eclipse phase* of infection, during which infectious virus cannot be recovered from the infected cell. Nucleic acids from RNA viruses and poxviruses assemble into nucleocapsids in the cytoplasm. For all DNA viruses except poxviruses, viral DNA assembles into nucleocapsids in the nucleus. In general, the capsid proteins of viruses with icosahedral nucleocapsids can self-assemble into densely packed and highly ordered capsid structures. Herpesviruses require an assemblin protein as a scaffold for capsid assembly. Viral nucleic acid then spools into the assembled capsid. For herpesviruses, a full unit of the viral DNA genome is packaged into the capsid, and a capsid-associated nuclease cleaves the viral DNA at both ends. In the case of viruses with helical nucleocapsids, the protein component appears to assemble around the nucleic acid, which contributes to capsid organization.

Viruses must egress from the infected cell and not bind back to their receptor(s) on the outer surface of the plasma membrane. Viruses can acquire envelopes from cytoplasmic membranes or by budding through the cell's plasma membrane. Excess viral membrane glycoproteins are synthesized to saturate cell receptors and facilitate separation of the virus from the infected cell. Some viruses encode membrane proteins with enzymatic activity for receptor destruction. Influenza virus, for example, encodes a glycoprotein with neuraminidase activity. Neuraminidase destroys sialic acid on the infected cell's plasma membrane so that newly released virus does not get stuck to the dying cell. Oseltamivir and zanamivir are neuraminidase inhibitors that are used to treat or provide prophylaxis for influenza virus infection. Herpesvirus nucleocapsids acquire an initial envelope by assembling in the nucleus and then budding through the nuclear membrane into the endoplasmic reticular space. The initially enveloped herpesvirus is then de-enveloped and released from the cell either by exocytosis or by re-envelopment at the plasma membrane. Nonenveloped viruses depend on the death and dissolution of the infected cell for their release.

FIDELITY OF VIRAL REPLICATION

Hundreds or thousands of progeny may be produced from a single virus-infected cell. Many particles partially assemble and never mature into virions. Many mature-appearing virions are imperfect and have only incomplete or nonfunctional genomes. Despite the inefficiency of assembly, a typical virus-infected cell releases 10–1000 infectious progeny. Some of these progeny may contain genomes that differ from those of the virus that infected the cell. Smaller, "defective" viral genomes have been noted with the replication of many RNA and DNA viruses. Virions with defective genomes can be produced in large numbers through packaging of incompletely synthesized nucleic acid. Adenovirus packaging is notoriously inefficient, and a high ratio of particle to infectious virus may limit the amount of recombinant adenovirus that can be administered for gene therapy since the immunogenicity of defective particles may contribute to adverse effects.

Changes in viral genomes can lead to mutant viruses of medical significance. In general, viral nucleic acid replication is more error-prone than cellular nucleic acid replication. RNA polymerases and reverse transcriptases are significantly more error-prone than DNA polymerases. Mutations can also be introduced into the HIV genome by APOBEC3G, a cellular protein that is packaged in the virion. APOBEC3G deaminates cytidine in the virion RNA to uridine. When reverse transcriptase subsequently uses the altered virion RNA as a template in the infected cell, a guanosine-to-adenosine mutation is introduced into the proviral DNA. Mutations resulting in less efficient viral growth, or fitness, may be detrimental to the virus. HIV-encoded Vif blocks APOBEC3G activity in the virion, inhibiting the debilitating effects of hypermutation on genetic integrity. Nevertheless, mutations resulting in evasion of the host immune response or resistance to antiviral drugs are preferentially selected in patients, with the consequent perpetuation of infection. Viral genomes can also be altered by recombination or reassortment between two related viruses in a single infected cell. Although this occurrence is unusual under most circumstances of natural infection, the genome changes can be substantial and can significantly alter virulence or epidemiology. Reassortment of the avian or mammalian influenza A hemagglutinin gene into a human influenza background can result in the emergence of new epidemic or pandemic influenza A strains.

VIRAL GENES NOT REQUIRED FOR VIRAL REPLICATION

Viruses frequently have genes encoding proteins that are not directly involved in replication or packaging of the viral nucleic acid, in virion assembly, or in regulation of the transcription of viral genes involved in those processes. Most of these proteins fall into five classes: (1) proteins that directly or indirectly alter cell growth; (2) proteins that inhibit cellular RNA or protein synthesis so that viral mRNA