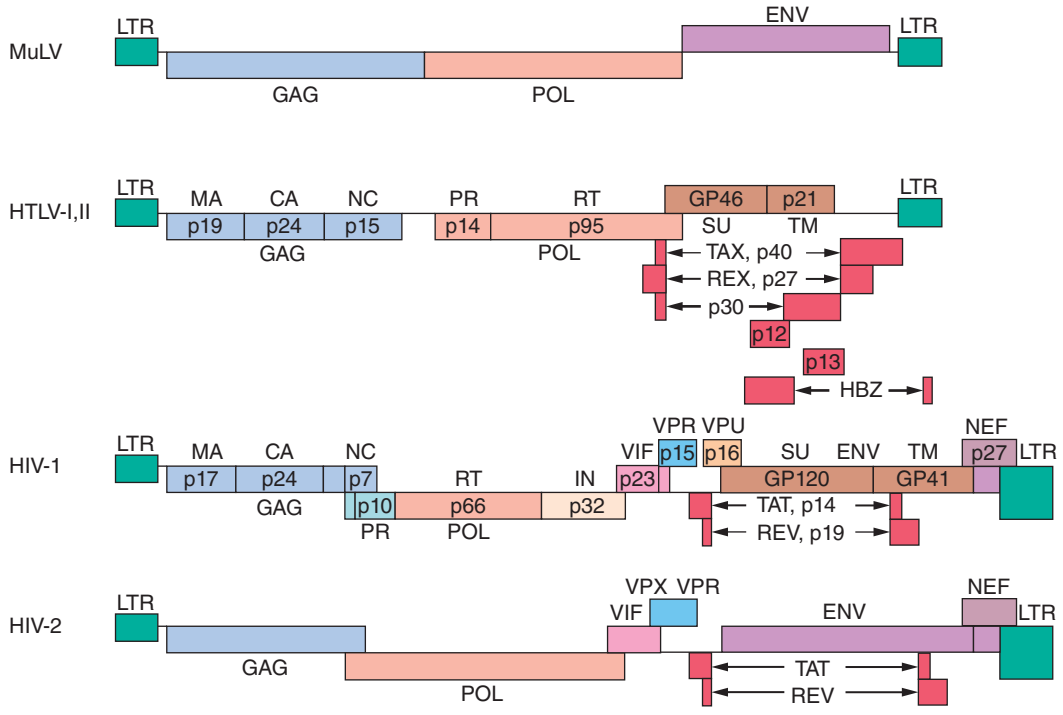

FIGURE 225e-2 Genomic structure of retroviruses. The murine leukemia virus MuLV has the typical three structural genes: *gag, pol*, and *env*. The *gag* region gives rise to three proteins: matrix (MA), capsid (CA), and nucleic acid–binding (NC) proteins. The *pol* region encodes both a protease (PR) responsible for cleaving the viral polyproteins and a reverse transcriptase (RT). In addition, HIV *pol* encodes an integrase (IN). The *env* region encodes a surface protein (SU) and a small transmembrane protein (TM). The human retroviruses have additional gene products translated in each of the three possible reading frames. HTLV-1 and HTLV-2 have *tax* and *rex* genes with exons on either side of the *env* gene. HIV-1 and HIV-2 have six accessory gene products: *tat, rev, vif, nef, vpr*, and either *vpu* (in HIV-1) or *vpx* (in HIV-2). The genes for these proteins are located mainly between the *pol* and *env* genes. GP, glycoprotein; HBZ, HTLV-1 basic leucine zipper domain–containing protein; LTR, long terminal repeat.

called *HTLV-1-associated myelopathy* (HAM). HTLV-1 may also play a role in infective dermatitis, arthritis, uveitis, and Sjögren's syndrome.

Two years after the isolation of HTLV-1, HTLV-2 was isolated from a patient with an unusual form of hairy cell leukemia that affected T cells. Epidemiologic studies of HTLV-2 failed to reveal a consistent disease association. Similarly, HTLV-3 and HTLV-4 have been identified but have no known disease association.

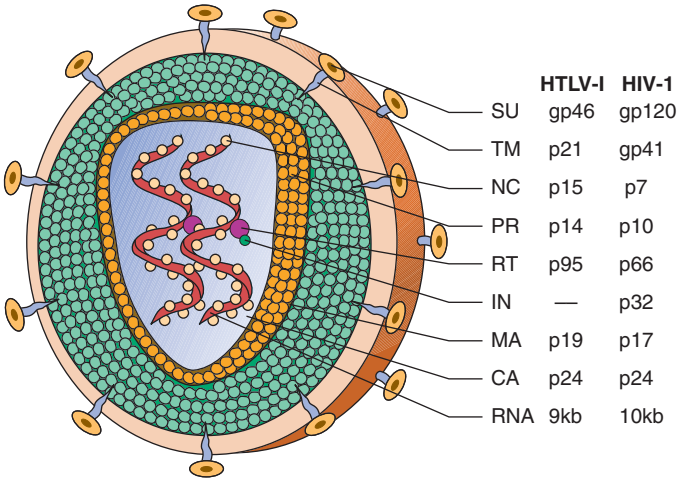

FIGURE 225e-3 Schematic structure of human retroviruses. The surface glycoprotein (SU) is responsible for binding to receptors of host cells. The transmembrane protein (TM) anchors SU to the virus. NC is a nucleic acid–binding protein found in association with the viral RNA. A protease (PR) cleaves the polyproteins encoded by the *gag, pol*, and *env* genes into their functional components. RT is reverse transcriptase, and IN is an integrase present in some retroviruses (e.g., HIV-1) that facilitates insertion of the provirus into the host genome. The matrix protein (MA) is a Gag protein closely associated with the lipid of the envelope. The capsid protein (CA) forms the major internal structure of the virus, the core shell.

BIOLOGY AND MOLECULAR BIOLOGY

Because the biology of HTLV-1 and that of HTLV-2 are similar, the following discussion will focus on HTLV-1.

Human glucose transporter protein 1 (GLUT-1) functions as a receptor for HTLV-1, probably acting together with neuropilin-1 (NRP1) and heparan sulfate proteoglycans. Generally, only T cells are productively infected, but infection of B cells and other cell types is occasionally detected. The most common outcome of HTLV-1 infection is latent carriage of randomly integrated provirus in CD4+ T cells. HTLV-1 does not contain an oncogene and does not insert into a unique site in the genome. Indeed, most infected cells express no viral gene products. The only viral gene product that is routinely expressed in tumor cells transformed by HTLV-1 in vivo is *hbz*. The *tax* gene is thought to be critical to the transformation process but is not expressed in the tumor cells of many ATL patients, possibly because of the immunogenicity of *tax*-expressing cells. Cells transformed in vitro, by contrast, actively transcribe HTLV-1 RNA and produce infectious virions. Most HTLV-1-transformed cell lines are the result of the infection of a normal host T cell in vitro. It is difficult to establish cell lines derived from authentic ATL cells.

Although *tax* does not itself bind to DNA, it does induce the expression of a wide range of host cell gene products, including transcription factors (especially c-rel/NF-κB, ets-1 and -2, and members of the fos/jun family), cytokines (e.g., interleukin [IL] 2, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor), membrane proteins and receptors (major histocompatibility [MHC] molecules and IL-2 receptor α), and chromatin remodeling complexes. The genes activated by *tax* are generally controlled by transcription factors of the c-rel/NF-κB and cyclic AMP response element binding (CREB) protein families. It is unclear how this induction of host