Chapter 1

INTRODUCTION

Summary

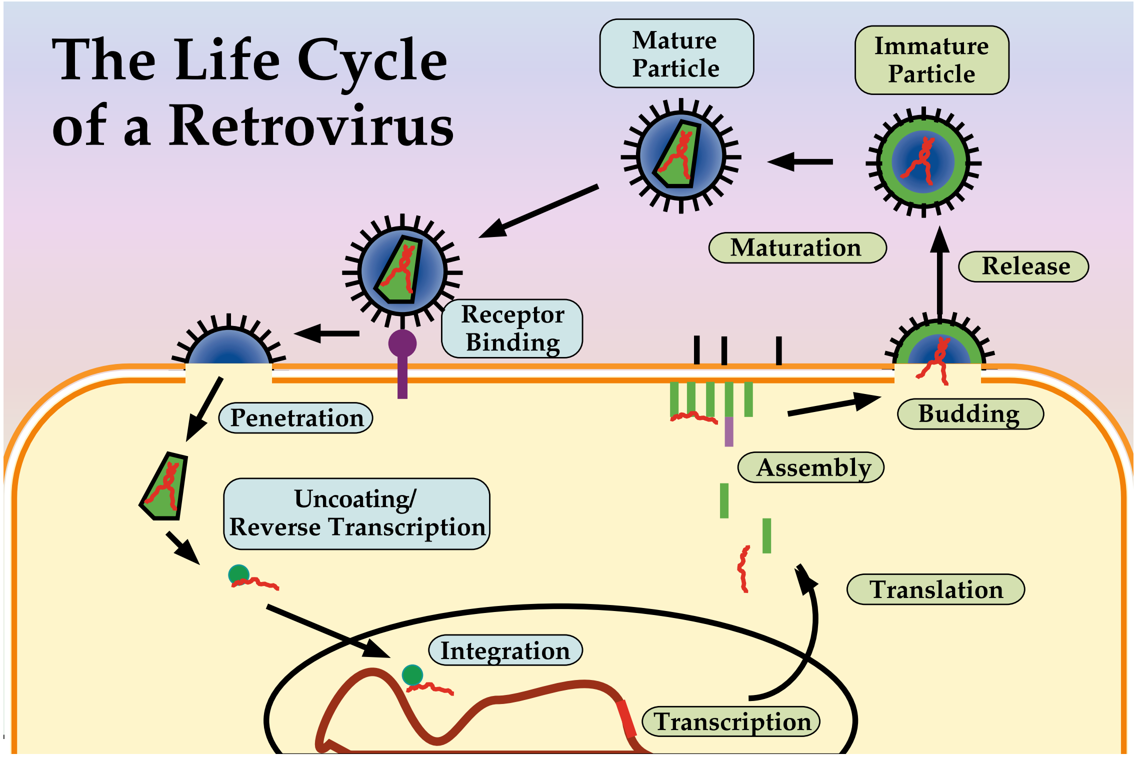
Viruses in the family *Retroviridae*, the retroviruses, have been found to play important roles in human disease. Human Immunodeficiency Virus Types 1 (HIV-1) and 2 (HIV-2), Human T-Cell Lymphoma Virus (HTLV) as well as human endogenous retrovirus (HERV) sequences are the causes of human diseases (30, 97). HIV-1 is the etiological agent of acquired immune deficiency syndrome (AIDS), which has become the fourth leading cause of mortality in the world today (1). Therapeutic drugs against HIV-1 to date have been targeted primarily at the stages of the viral life cycle involved in the reverse transcription of the virus in host cells and most recently at the maturation of infectious virus particles (46). Relatively little is known about the processes of virus assembly that occur in infected cells to produce virus progeny capable of propagation.

Due to the nature of their life cycle and their permanence in the host cell's genome, retroviruses also have become a valuable tool in the development of vectors for use in gene therapy protocols for the treatment of disease . Retroviral vectors can be designed to target specific cell types and a number of approaches have been employed that allow regulation of gene expression. In addition to their clinical importance, retroviruses have been employed for numerous laboratory uses such as transduction of exogenous genes, insertional mutagenesis in eukaryotic models, cell fate determination during organism development and cDNA library construction (103).

Retroviruses are enveloped viruses containing two copies of single-stranded RNA genomes which encode three primary genes, *gag*, *pol* and *env*. The surface of the virus is covered by products of the *env* gene which are involved in binding and entry into the target cell. The inner core structure of the virus is formed by the product of the *gag* gene and ranges in shape from spherical to conical (30). The *pol* gene encodes the reverse transcriptase (RT) and an integrase (IN) protein which allow the retrovirus its unique lifestyle by transcribing the RNA genome into DNA and incorporating it into the genome of the host cell. In most retroviruses the *pol* gene also encodes a protease (PR) responsible for viral maturation (30). This thesis deals with the human immunodeficiency virus type 1 (HIV-1), a member of the lentivirus subfamily, and the Moloney Murine Leukemia Virus (M-MuLV), a type C retrovirus. Specific attention will be given to these two viruses throughout this introduction.

Overview of the Retroviral Life Cycle

The life cycle of a prototypic retrovirus (see Figure 1) begins when a mature, infectious particle encounters a target cell with the appropriate receptor(s) on its surface. The viral envelope glycoproteins bind to this receptor which causes a conformational change in the envelope to expose a fusion domain that allows fusion of the viral membrane with that of the host cell (79). HIV-1 has two receptors, the CD4 glycoprotein, and members of the chemokine receptor family. Binding of the envelope protein to the CD4 exposes regions of the envelope which bind to the chemokine receptor and expose the fusion domain



(157). The receptor for the ecotropic M-MuLV envelope is a cationic amino acid transporter (79).

After the viral membrane has fused with the host cell membrane, the viral nucleocapsid structure is deposited in the host cell cytoplasm and uncoats there