Papovaviruses

Figure 13 Structure and genome organization of the papovavirus simian virus 40. (A) The virion. (Left) Electron micrograph of negatively stained simian virus 40 virions. Magnification, ×625,000. From F. A. Andered et al., *Virology* **32**:511–523, 1967, with permission. (Right) Diagram of the virion, showing the names and locations of virion proteins and the organization of the 5,243-bp, circular, double-stranded DNA genome into approximately 25 nucleosomes by the cellular histones H2A, H2B, H3, and H4 (the core histones). One molecule of either VP2 or VP3, which possess a common C-terminal sequence (B), is believed to be associated with each VP1 pentamer. **(B) Genome organization.** Locations of the origin of viral DNA synthesis (Ori) and of the early and late mRNA sequences encoding the large and small T antigens (LT and sT) and the virion structural proteins VP1, VP2, and VP3 are indicated. The late mRNA species generally contain additional open reading frames in their 5′-terminal exons, such as that encoding leader protein 1 (LP1).

Figure 14 Single-cell reproductive cycle of simian virus 40. The virus attaches to permissive monkey cells upon binding of VP1 to a receptor on the surface of the cell. Polyomavirus, but not simian virus 40, employs cell surface sialic acid residues for attachment. The virion is deposited in the cytoplasm **(step 1)** following entry. It is transported to the nucleus and uncoated **(2)** to release the viral genome packaged by cellular nucleosomes. The **early** transcription unit is transcribed by host cell RNA polymerase II **(3)**. After alternative splicing and export to the cytoplasm **(4)**, the early mRNAs are translated by free cytoplasmic ribosomes into the early proteins LT and sT **(5)**. The former is imported into the nucleus **(6)**, where it binds to the simian virus 40 origin of replication to initiate viral DNA synthesis **(7)**. Apart from LT, all components needed for viral DNA replication are provided by the host cell. As they are synthesized, daughter viral DNA molecules are packaged by cellular nucleosomes to form the viral nucleoproteins often called minichromosomes. LT also stimulates **late** transcription from replicated viral DNA templates **(8)**. Processed late mRNAs are exported to the cytoplasm **(9)**, in which the virion structural proteins VP1, VP2, and VP3 are synthesized from them **(10)**. These structural proteins are imported into the nucleus **(11)** and assemble around viral minichromosomes to form progeny virions **(12)**. Virions are released by an unknown mechanism **(13)**.

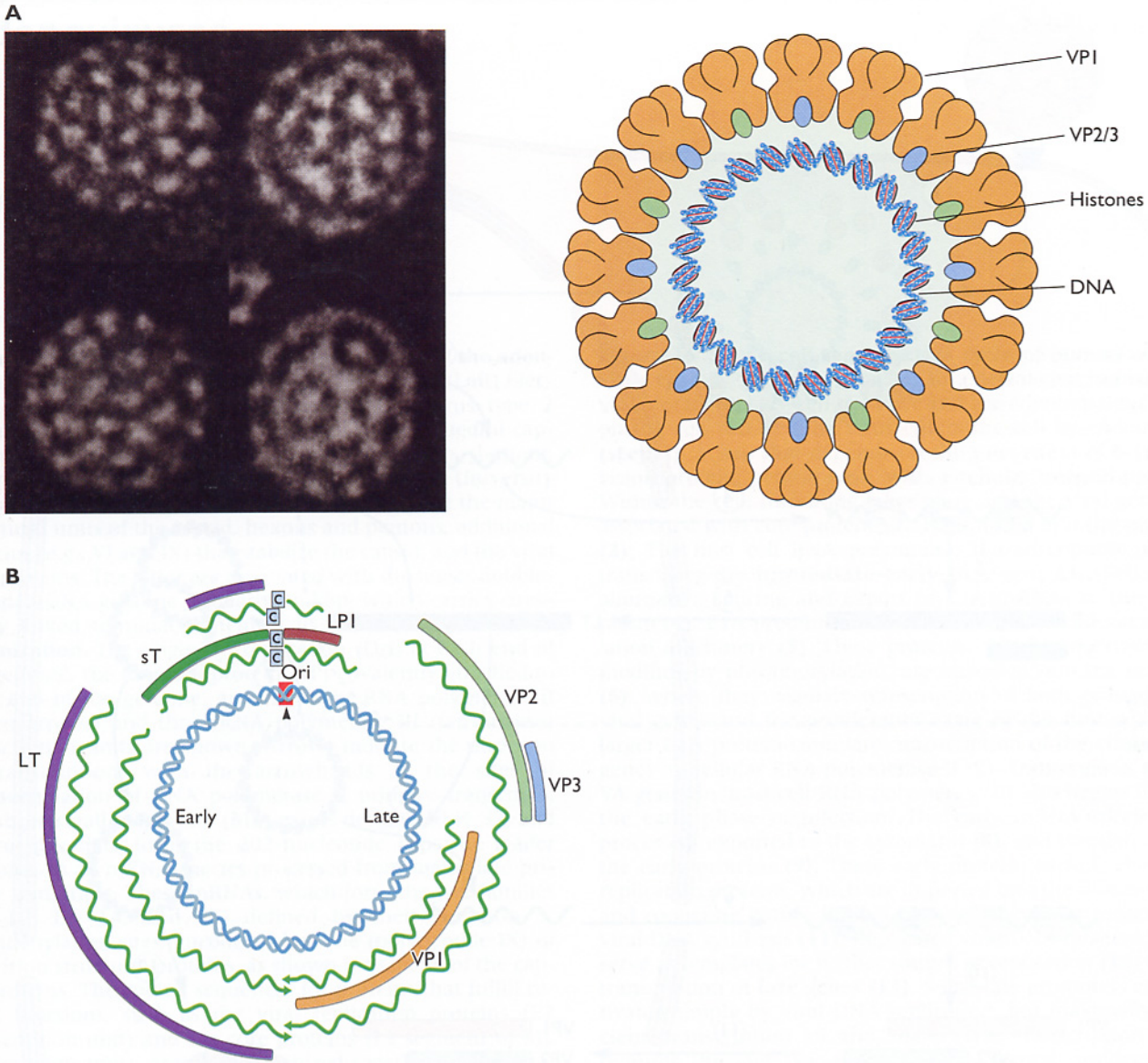

Figure 13 Structure and genome organization of the papovavirus simian virus 40.

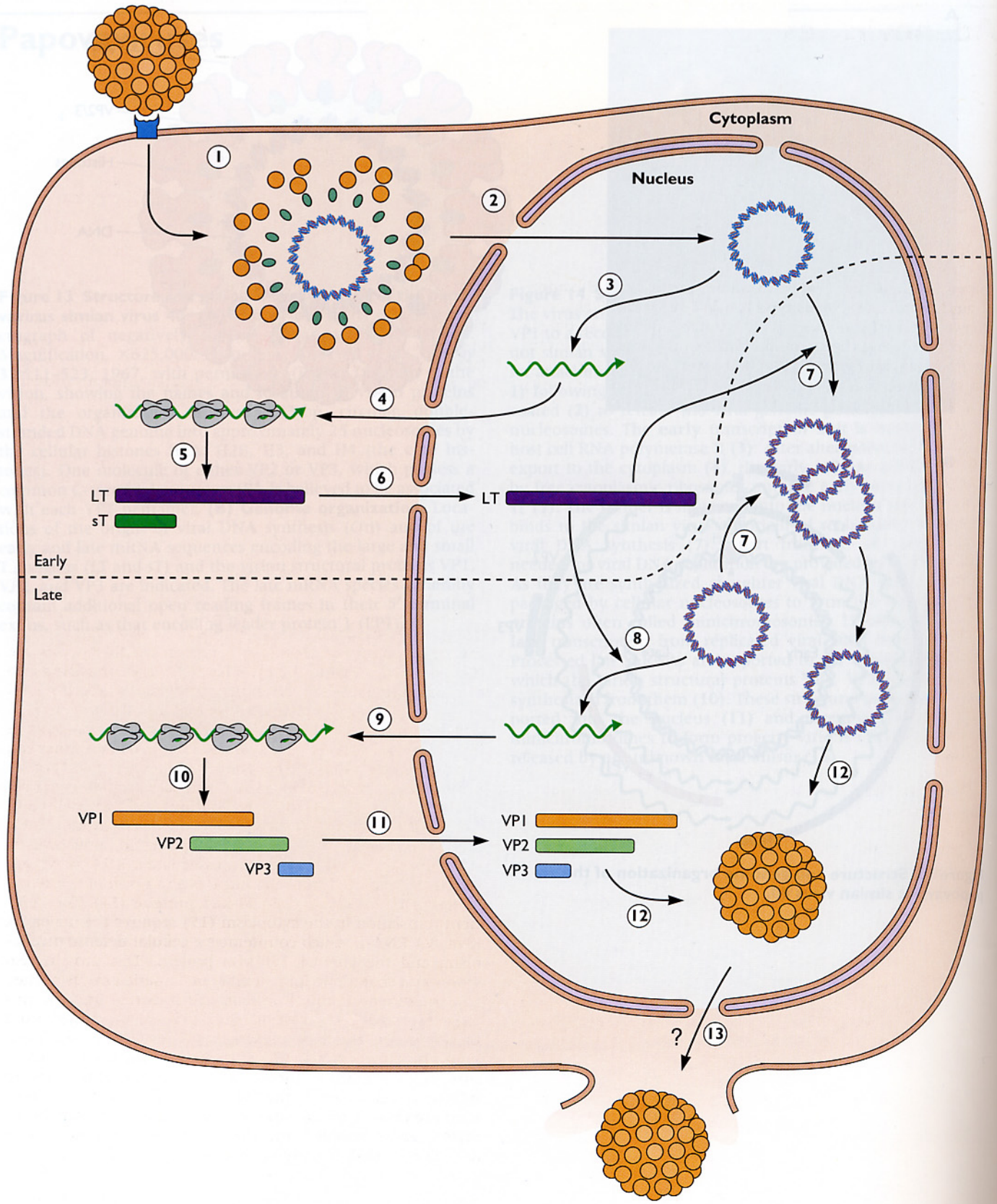

Figure 14 Single-cell reproductive cycle of simian virus 40.

fission yeast have provided (143). The ability to identify critical regulatory activities through mutation, to identify the genes that specify these activities, and then to understand the biochemical mechanisms of action of these gene products has been enormously productive. Although the study of the cell cycle in mammalian cells clearly suffers from the limited genetic analysis possible in mammalian systems, studies of the oncogenic action of the proteins encoded by the tumor viruses, particularly the DNA tumor viruses, have provided important insights into the mechanisms controlling mammalian cell growth. Such studies have helped to elucidate roles for the retinoblastoma and p53 tumor-suppressor proteins as regulators of mammalian cell growth (Fig. 1). Each of these proteins controls the progression of cells through the G_1 phase of the cell cycle. The p53 gene plays an additional role in triggering programmed cell death (apoptosis) in response to various signals. In each case, DNA tumor virus oncoproteins act to inhibit the action of these two key tumor-suppressor proteins, thereby driving an otherwise quiescent cell to enter S phase. Indeed, this is the key to understanding the link between the replication strategy of the DNA tumor viruses and their oncogenic potential. The natural host cell for the viruses is a quiescent, differentiated cell that presents an environment that is not conducive to viral DNA replication. Thus the strategy of these viruses is to alter this environment, by deregulating the normal cell-cycle control of entry to S phase to induce the genes encoding activities necessary for DNA replication. In the normal replicative infection by these viruses, this cell-cycle deregulation is of no consequence because the infected cell eventually dies. However, when the infection is in some way impaired, then the events causing deregulation of the cell cycle contribute to oncogenic transformation.

In many respects, the virus-mediated disruption of a cell growth control pathway is analogous to the genetic analysis afforded by yeast. For instance, the inactivation of p53 function through the action of the adenovirus E1B protein is, in principle, equivalent to the isolation of a p53 mutant cell; in essence, the viral protein is a mutagen. Moreover, the ability to understand this "mutation" in the context of a viral infectious cycle provides an additional physiologic context, the evolution of a viral replication strategy, in which to view the mutation.

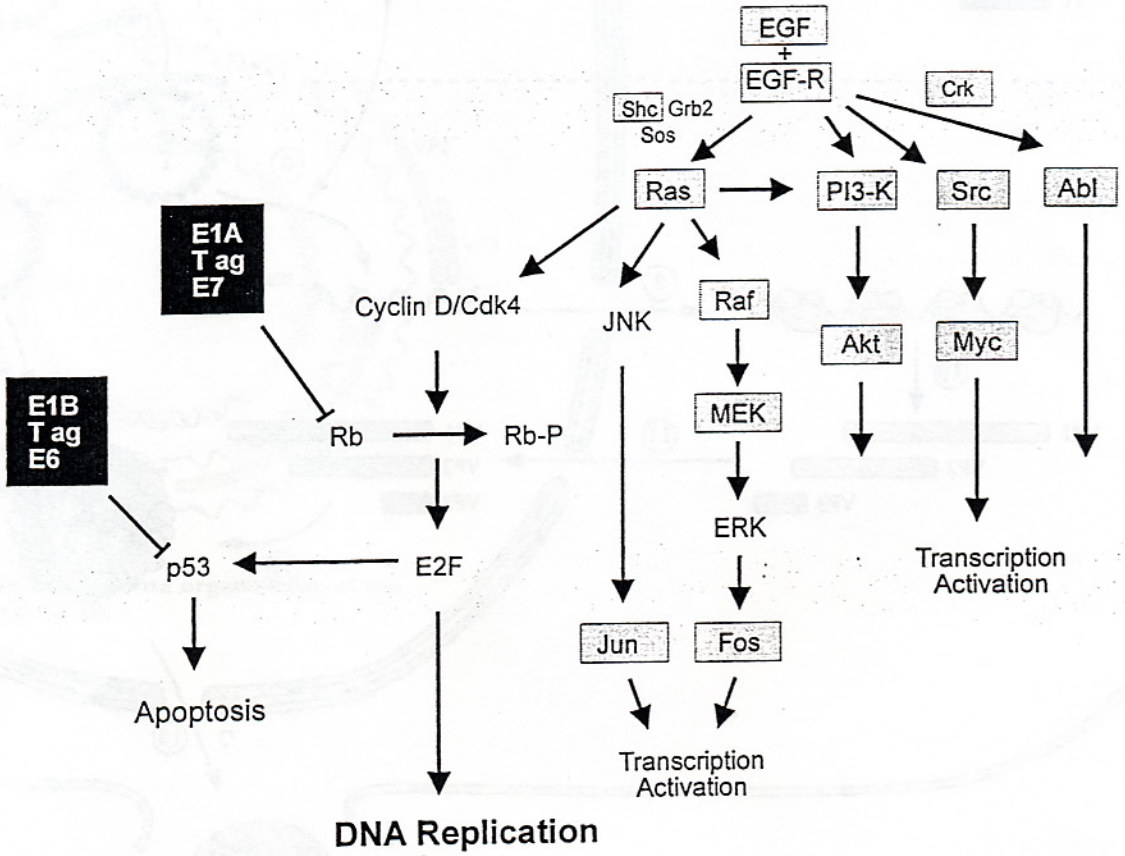

FIG. 1. Cell growth-regulatory pathways, activated by growth factor–receptor activation, which are targets of viral oncoproteins. The DNA tumor virus oncoproteins (*black boxes*) target the Rb and p53 tumor suppressors, leading to an inactivation of their function and deregulation of the G_1 cell-cycle pathway and the apoptotic response pathway. In contrast, the transforming genes found in the RNA tumor viruses (*gray boxes*) represent activated oncogenes, encoding various proteins that function in growth factor–signaling pathways.