Viral Infection: Receptors

- **Receptors:**
  - **Identification of receptors has come from expressing the gene for the receptor in a cell to which a virus does not normally bind -OR-**
  - **By blocking virus attachment with a monoclonal antibody**
- **Viruses bind up to 3 different receptors and co-receptors (low affinity→ primary→ co-receptor)**
  - **Receptors serve to overcome any repulsive forces that may exist between virus and cell and to trigger release of viral genome into cell**

- **Virus in fluid outside side will 1st come in contact with low affinity receptor on membrane**
  - **Virus will roll along the outside of the cell contacting these low affinity receptors, breaking away and finding others until it finds a primary, high affinity, receptor. If primary receptor is not found it will dissociate and try again. (HIV first binds to low affinity heparan sulphate receptor until it finds the high affinity CD4 receptor, and cannot bind to CD4 unless it has bound to heparan first). Heparan may cause a conformational change in gp-120 so it can bind to CD4.**
  - **This causes further conformational changes and allows gp-120/heparan/CD4 to bind to co-receptor CCR5 or CXCR4**
- **This series of binding steps acts as a fail-safe mechanism that tells the virus that it has bound to a cell that will be able to replicate the genome**

- **Entry of virus into cell**
  - **Plasma membrane is fluid and active. Endocytosis occurs all the time (membrane invaginates and a vesicle is pinched off into cytoplasm**
  - **Virus will need to recruit more receptors in order to enter the cell and then to be uncoated (*receptor mediated endocytosis*)**
- **Uncoating**
  - **Some enveloped viruses (HIV-1) uncoat by fusion of the lipid bi-layer of virus with that of the target cell**
  - **Other enveloped viruses and all non-enveloped viruses are taken up by receptor-mediated endocytosis**

- Release of the genome into the cytoplasm
  - Dependent upon a decrease in pH to 5-6
  - Achieved by fusion with endosome
  - Causes conformational alterations in membrane and capsid
- Nucleoprotein (not naked nucleic acid) is released into cell -- this protects viral NA
  - There is secondary uncoating of the NA by removal of proteins

- **Most of NA of viral origin is degraged**
  - With poliovirus virus:cell ratio must be 1000:1

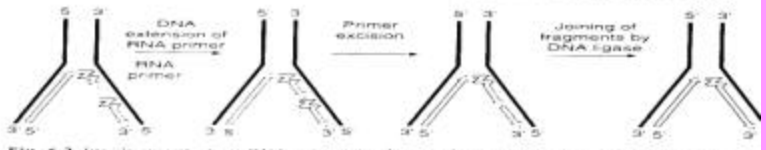
- **Infection of plants**
  - Virus must traverse cell wall: traumatic event or vectors to cause mechanical damage

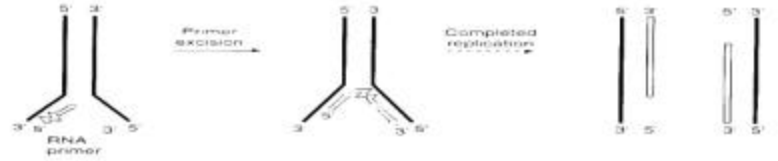
- **Bacteriophage Infection**
  - Most attach to cell wall, but there are receptors on pili, flagella and capsule
  - Attachment of virus by tail fibers
    - After attachment the tail fibers bend at center to bring virus closer to cell
    - When base plate is ~ 10 nm from cell wall contact is made by the short pins on the plate
    - Tail contracts by compression of ring-type proteins, and the tail core (which does not contract) is forced through the cell wall with a twisting motion
    - Contraction of the head results in movement of NA into bacterial cell
    - This process is aided by 144 ATP molecules and lysozyme

- **Replication of Viral DNA**
  - **Same as for cellular DNA**
    - **DNA polymerase copies a template strand, beginning from the 3' end of the template (synthesis of new strand occurs in the 5'→3' direction)**
    - **From Meselson-Stahl experiment showing "semi-conservative replication" in a discontinuous manner of ds linear DNA. Ligase enzymes link Okazaki fragments**
  - **DNA polymerases are unable to start DNA chains *de novo*, all require a hydroxyl group to act as a primer, and RNA polymerase is used to initiate this process because it does not require the hydroxyl group. Thus, there is a short RNA template at the beginning of DNA synthesis.**
  - **DNA polymerases have greater "Fidelity" than RNA polymerases**

- **The RNA primer then is digested away. This results in progressive shortening of the DNA molecule since DNA is not made to fill in the RNA template.**
  - **This problem of continued shortening of DNA is solved by TELOMERASE enzymes. There are telomeres at either end of the linear molecule that help to maintain the length of the DNA (repeated sequences at either end)**
- **Certain viruses have adapted their genome to be circular, which by-passes this problem of shortening of the chromosome (may be circular to begin with or circularize as an intermediate structure)**

THE PROCESS OF INFECTION: HA





- **SV40 is best studied virus for DNA replication**

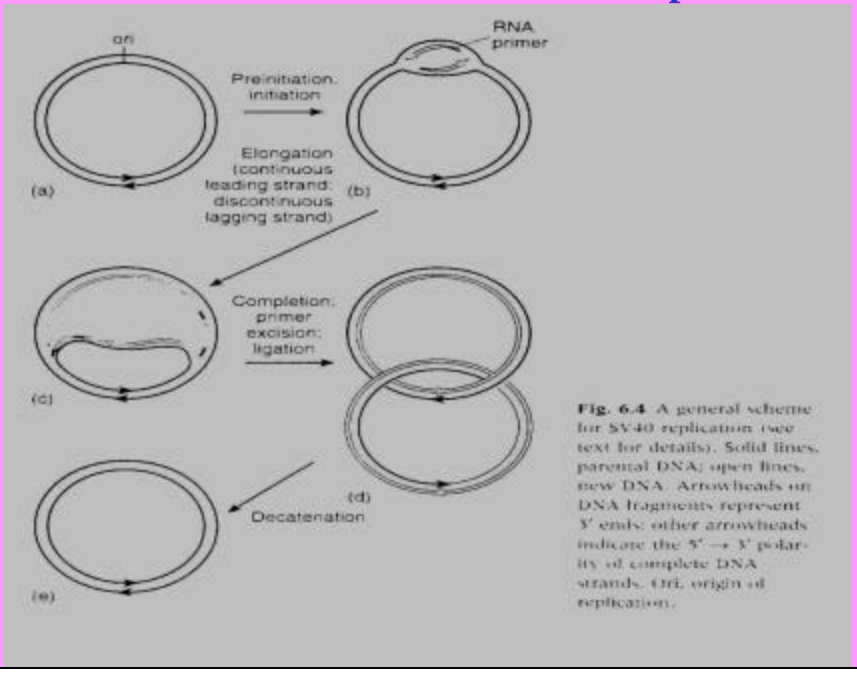


Fig. 6.4 A general scheme for SV40 replication (see text for details). Solid lines, parental DNA; open lines, new DNA. Arrowheads on DNA fragments represent 3′ ends; other arrowheads indicate the 5′ → 3′ polarity of complete DNA strands. Ori, origin of replication.

- **Circular genome has a single POINT of ORIGIN**
  - **Synthesis begins on BOTH strands and proceeds in opposite directions**
  - **Replication forks diverge from point of origin and RNA primers are digested. Structure appears as Greek "theta structure"**
  - **Replication forks meet at opposite end, and when they do both strands have been completely copied**
  - **Circles then have to separate**
- **Large T Antigen provides recognition of the Origin and begins the separation of the DNA strands**