Danger from the Wild: HIV, Can We Conquer It?

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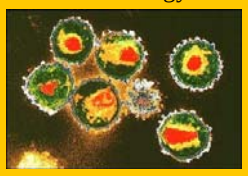
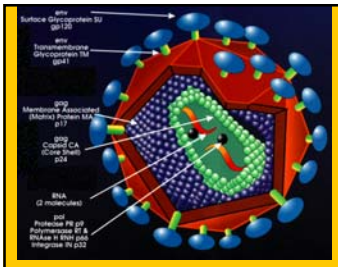


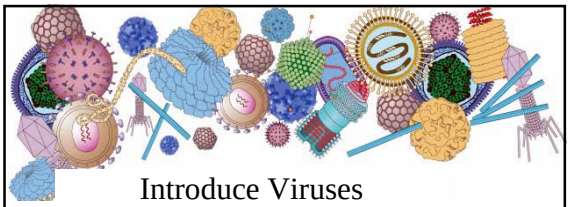


Part I

Viruses: HIV and non-equilibrium viruses

Introduce Viruses

- A separate kingdom of the living world
- Very small objects that can duplicate themselves only by penetrating living cells and diverting the cell's macromolecular syntheses towards making more virus

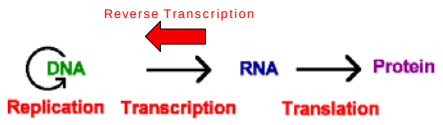


Introduce Viruses

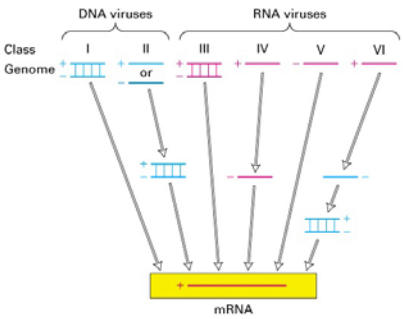
They can have RNA or DNA as their genetic material and can grow in all kinds of cells: animal, plant and even bacterial (bacteriophages)

Central Dogma of Molecular Biology

Updated Dogma (1970)



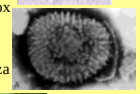
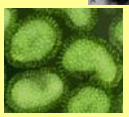
Classifying Viruses by How They Relate to mRNA



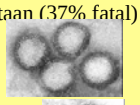
Viruses in the News



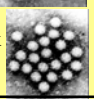
- HIV
- SARS
- Smallpox
- Influenza

- Marburg (1967, 31 cases, 7 deaths)
- Ebola (1976, 500 cases, 460 deaths)
- Hantaan (37% fatal)



- Norwalk



Much of molecular biology derived from studying viruses

Bacterial viruses (bacteriophage)

- Hershey and Chase showed that DNA is the hereditary material
- Luria and Delbruck showed that mutations pre-exist before evolutionary selection
- Meselson and Stahl showed DNA replicated by copying of each strand into a duplex
- Hershey and Benzer showed that genes had fine structure
- Brenner et al showed that messenger RNA carried information from DNA to protein

Much of molecular biology derived from studying viruses

Mammalian viruses

- Splicing of nuclear RNAs to generate messenger RNA
- Discovery of reverse transcription

Plant Viruses

- RNA is able to act as genetic material(evolution went through an RNA world)
- Protection against pathogens by interfering RNA

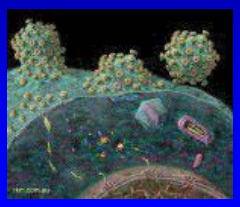
Many different kinds of viruses

- The number of viruses is uncountable because each kind of plant, bacterium and animal has its own set of viruses
- Now recognize 1,550 species of viruses

Growth of Viruses

- Viruses only grow inside of cells (plants, animals, bacteria)
- They multiply very fast, some can increase by 1000-fold in 6 hours
- Most can only continue to live if they are passed from host to host organism
- So we can eradicate ones that are obligately human like smallpox and polio

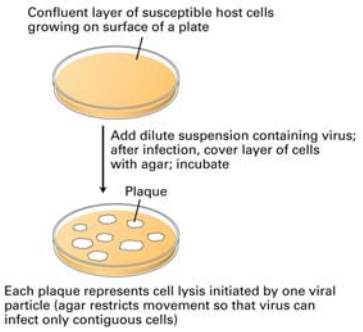
Viruses develop inside cells and either bud from the cell surface, taking the cell membrane with them or cause the cell to burst, liberating virus particles from the cell interior.



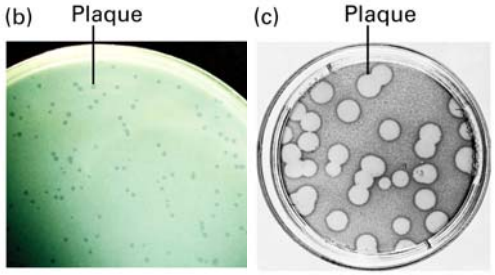
Viruses only made sense when molecular biology was born

- Viruses are so small that generally consist of nothing but genetic instructions (DNA or RNA) and a protective protein coat
- Some have a few other proteins that help initiate the infection
- So viruses could not be understood until the basic tenets of molecular biology were established

Plaque assay determines the number of infectious particles In a viral suspension



Plaques formed by bacteriophage lamba plated on *E. coli* (b) or poliovirus plated on HeLa cells (c)



Equilibrium and Non-Equilibrium Viruses

- Equilibrium viruses have been long term parasites of a given species
  - They are generally not lethal but spread well
  - The common cold is best example

Equilibrium and Non-Equilibrium Viruses

- Non-equilibrium have jumped from another species and are not adapted to the new host
  - They are sometimes very lethal, may spread poorly or well, and represent most of our difficult problem viruses

Examples of Equilibrium and Non-Equilibrium Human Viruses

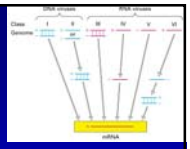
Equilibrium
- Polio
- Smallpox
- Common cold
- Measles
- Herpes

Non-equilibrium
- Influenza (birds)
- HIV (chimp)
- SARS (bats?)
- Ebola (bats)
- Hantaan (rodent)

Turning to HIV

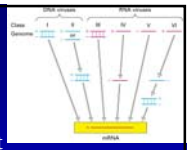
HIV only made sense when reverse transcription was discovered because it was HIV's reverse transcriptase that revealed its existence as a virus.

Discovery of Reverse Transcription



- In 1960, when I entered the field of molecular biology, we knew two polymerases: DNA polymerase for replication and DNA-dependent RNA polymerase for transcription
- In 1962 we found RNA-dependent RNA polymerase in poliovirus-infected cells
- In 1969 we found that negative strand viruses exist and we discovered the polymerase that copies the negative strand in the virus particle

Discovery of Reverse Transcription



- In 1960's Howard Temin speculated that RNA tumor-causing viruses could turn their RNA into DNA (which would solve the problem of the stability of cancers)
- In 1970, Howard and I independently discovered that the RNA tumor virus particles contained a RNA-dependent DNA polymerase (reverse transcriptase)
- In 1975 we shared the Nobel Prize in Physiology or Medicine for our discovery (with Renato Dulbecco who had been a mentor to both of us)

Reverse transcriptase

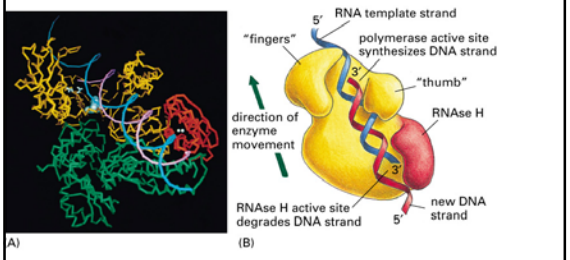
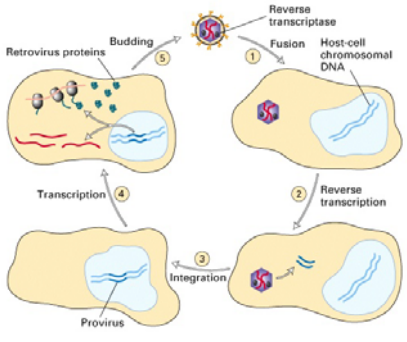


Figure 5–74. Molecular Biology of the Cell, 4th Edition.

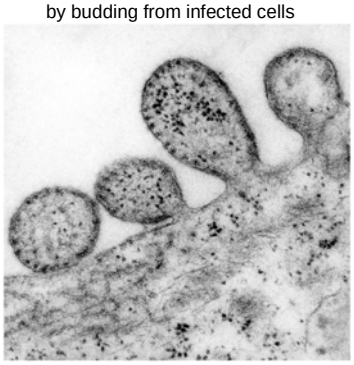
Implications of the Discovery of Reverse Transcription

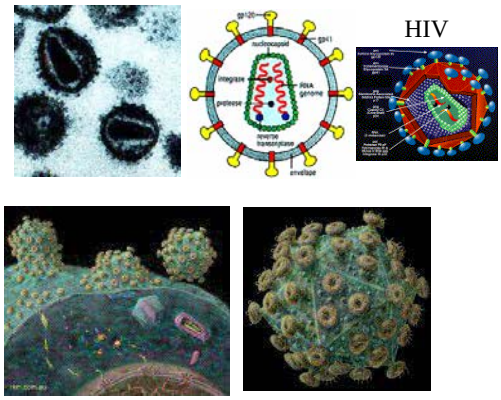
- RNA tumor viruses became retroviruses
- Cancer can be caused by the permanent association of new genes with a cell (cancer is genetic-- occurs most often by mutation of normal genes to form cancer-causing genes)
- Can capture cellular genes by reverse transcription of messenger RNA (started biotechnology)
- Much (45%) of the human genome arose by reverse transcription (mobile genetic elements)
- HIV found to be a retrovirus (discovered by polymerase in 1982)

Life Cycle of a Retrovirus (HIV)



Progeny virions of enveloped viruses are released by budding from infected cells





The Awful Statistics, 2005

- **65 million people have been infected, 25 million dead and 40 million living with AIDS (5 million in India; 0.8 million in China)**
- **13,000 infections/day; 4.9 million/year**
- **3.1 million dying per year-- as much as tuberculosis or malaria**
- **Life expectancy in numerous African countries reduced by >20 years**

Why is HIV Lethal?

- **HIV is a classic non-equilbrium virus**
- **It is actually endemic in African great apes (chimpanzees) and got a foothold in the human population around 70 years ago**

Why is HIV Lethal?

- **It grows in one of the key cell types of our immune systems, the helper T cell, and kills them**
- **Infected people lose their helper T cells slowly, over years, ultimately become immunodeficient and die from infections by organisms that healthy people easily fight off**