Viral GENETICS –Sherris Medical Microbiology

- viruses generally use two mechanisms – **MUTATION** and **RECOMBINATION** – by which viral genomes change during infection and there are virologic, immunologic, and medical consequences of some of these changes.

- Majority of the human virus particles from an infected cells are DEFECTIVE.

Typically, the majority of the particles derived from a cell infected with a human virus are NONinfectious in other cells as determined by a plaque assay … it is clear that many defective particles are being produced ! this production of defective particles arises because the mutation rates for human viruses are usually high and because many infections occur at high multiplicities, where defective genomes are complementary by non-infective viruses and therefore propagated.

1 [MUTATION]

- Many DNA viruses use the host DNA synthesis machinery for replicating their genomes. Therefore they benefit from the error correcting mechanisms used by the cell.

- the large human viruses (Adenoviruses, Herpesviruses, and Pox viruses) code for their own DNA polymerases. And these enzymes are not as effective at proofreading as the cellular polymerases.

- the resulting higher error rates in DNA replication endow the viruses with the potential for a high rate of evolution, but they are also partially responsible for the high frequency of defective viral particles.

- the replication of RNA viruses is characterized by even higher error rates because viral RNA polymerases do not posses any proofreading capabilities.

- even for the smallest RNA viruses, virtually every round of replication introduces one or more nucleotide changes somewhere in the genome.

- because of the redundancy in the genetic code, some mutations are silent and are not reflected in changes at the protein level, but many occur in essential genes and contribute to the large number of defective particles found for RNA human viruses.

- High mutation rates permit adaptation to changed conditions.

- the high mutation rates found for RNA viruses endow them with a Genetic PLASTICITY that leads readily to the occurrence of genetic variants and permits rapid adaptation to new environmental conditions.

- the large number of serotypes of Rhinoviruses causing the common cold, for instance, likely reflects the potential to vary by mutation.

- POINT Mutations occur in most RNA viruses and some DNA viruses as a result of errors caused by RNA or DNA polymerases due to lack of proofreading ability of the enzymes. Accumulation of point mutations in the viral genome may result in change of amino acids resulting in antigenic variation, which may allow the new viral variants to escape preexisting immunity.

- Mutations are responsible for antigenic drift in Influenza viruses.

- point mutations accumulate in influenza genes coding for the two envelope proteins (HEMERGGLUTANIN and NEURAMINDASE), resulting in changes in the antigenic structure of the virions. These changes lead to new variants not recognized by the immune system of previously infected individuals, this phenomenon is called ANTIGENIC DRIFT.

- the domains of the two envelope proteins that are most important for immune recognition are not essential for virus entry, so can tolerate amino acid changes leading to antigenic variations. This feature may distinguishes influenza from other human RNA viruses that passes the same high mutation rate but don't exhibit such high rates of antigenic drift.

- antigenic drift in epidemic influenza viruses from year to year requires continual updating of the strains used to produce annual influenza vaccines.

- High rates of mutation in Retroviruses are due to error-prone reverses transcriptase.

- the previously mentioned enzyme converts Retroviral RNA into double stranded DNA.

- after the viral DNA has integrated into the chromosome of the host cell, the retroviral DNA is transcribed by the host RNA polymerases II, which is also capable of generating errors. (ex; HIV-1). HIV-1 exhibits a high rate of mutation, and this properly gives HIV-1 the ability to evolve rapidly in response to changing conditions in the infected host.

- HIV-1 antigenic variation makes vaccine development difficult.

- Defective Interfering Particles accumulate at high multiplicities of infection.

- the noninfectious genome interfere with the replication of the infectious virus and so are called DEFECTIVE INTERFERING (DI) Particles.

- Deletions result from mistakes in replication, recombination, or the dissociation-reassociation of replicases.

- all RNA replicases have a tendency to dissociate from the template RNA, but remain bound to the end of the growing RNA chain.

By reassociating with the same or a different template at a different location, the replicase "finishes" replication, but, in the process creates a shorter or longer RNA molecules.

- Because the deletion variants in the population require less time to complete a replication cycle, they eventually predominate and constitute the DI particles.

- Defective Interfering Particles compete with infectious particles for replication enzymes.

- interference occurs because the DI particles successfully compete with the nondefective genomes for a limited supply of replication.

- the virions released at the end of the infection are therefore enriched for the DI particles. With each successive infection, the DI particles predominates over the normal particles as long as the multiplicity of infection is high enough that every cell is infected with at least one normal infectious particle.

If this condition is satisfied, then the normal particle can "complement" any defects in the DI particles and provide all of the viral proteins required for the infection.

2 [RECOMBINATION]

- Beside mutation, genetic recombination between related viruses is a major source of GENOMIC VARIATION.

- bacterial cells as well as the nuclei of human cells contains the enzymes necessary for homologous recombination of DNA. Thus, it is not surprising that recombinations arise from MIXED INFECTIONS involving two different strains of the same type of DNA virus.

- Homologous recombination is common in DNA viruses.

- Recombination for viruses with segmented RNA genomes involves reassortment of segments.

- Segment reassortment in mixed infections probably accounts for ANTIGENIC SHIFTS in influenza virus.

- reassortment occurs when two closely related segmented viruses infect the same cell, resulting in drastic antigenic changes and formation of new viral strains.

- reassortment of newly synthesized RNA segments generates parental types, new hybrid viruses, and hundreds of other possible combinations some of these hybrid viruses could become new strains causing sever epidemics or pandemic influenza.

- reassortment during infection of the same cell by human and certain animal influenza viruses is believed to account for the occasional drastic changes in the antigenicity of the human influenza A virus, these dramatic changes called ANTIGENIC SHIFTS produce strains to which much of the human population LACKs Immunity.

(eg; human flu virus and swine flu virus infect the lung cell of swine. Progeny viruses are assembled as a result of reassortment of newly synthesized RNA segments that may come from both viruses.)

- Poliovirus RNA genome is Not segmented.

- The second mechanism of RNA virus recombination is exemplified by the genetic recombination between different forms of poliovirus.

- Poliovirus replicase switches template to generate recombination.

- recombination occurs during replication by a "Copy Choice" type of mechanism.

During RNA synthesis, the replicase dissociates from one template and resumes copying a second template at the exact place where it left off on the first. The end result is a progeny RNA genome containing information from two different input RNA molecules. Strand switching during replication. Therefore generates a recombinant virus.

- early after infection, the reverse transcriptase within the virions synthesizes a DNA copy of the RNA genome by a process called reverse transcription.

In the course of reverse transcription, the enzyme is required to "JUMP" between two sites on the RNA genome. this propensity to switch templates apparently explains how the enzyme generates recombinant viruses.

- the Diploid nature (each particle carries two copies of the genome) of RETROviruses permits template switching and recombination during DNA synthesis.

- Occasional incorporation of the host mRNA into retroviral particles may produce oncogenic variants.

- Animal retroviruses package a cellular mRNA into the virion rather than a second RNA genome. This arrangement can lead to copy choice recombination between the viral genome and the cellular mRNA. The end result is, sometimes, the incorporation of a cellular gene into the viral genome.

This mechanism is believed to account for the production of highly oncogenic retroviruses containing modified cellular genes.