Viral Genetics

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ORIGIN OF VIRUSES

There are two widely accepted hypotheses: viruses are either wild genes or degenerated cells.

It is possible for pro- or eukaryotic cells to produce virusesThat lacked a lot of their biological activities (degeneracy).

Alternatively, some nucleic acid might have been transferred accidentally into a cell of a different species (e.g. through a wound or by sexual contact) and, instead of being degraded, as would normally be the case, might have survived and replicated (*escape*).

Viral Genetics

- The study of viral genetics falls into two general areas:
- (1) mutations and their effect on replication and pathogenesis.
- (2) the interaction of two genetically distinct viruses that infect the same cell.

MUTATIONS

Mutations in viral DNA and RNA occur by the same processes of base substitution, deletion, and frameshift. The most important practical use of mutations is in the production of vaccines containing live, attenuated virus. These attenuated mutants have lost their pathogenicity but have retained their antigenicity; therefore, they induce immunity without causing disease.

MUTATIONS

- There are two other kinds of mutants of interest.
- The first are **antigenic variants** such as those that occur with -influenza viruses, which have an altered surface protein and are not inhibited by preexisting antibody. The variant can thus cause disease, whereas the original strain cannot.
- - immunodeficiency virus and hepatitis virus also produce many antigenic variants. These viruses have an **“error-prone” polymerase** that causes the mutations.
- The second are **drug-resistant mutants**, which are insensitive to an antiviral drug because the target of the drug, usually a viral enzyme, has been modified

MUTATIONS

- **Conditional lethal mutations**
- **Determine the function of viral genes by using conditional lethal mutations, which are extremely valuable**
- - Under favorable conditions, these mutations are functional, but under limiting ones, they are unable to replicate or express the mutant gene..
- -Temperature-sensitive mutants of influenza virus are now being useto make a vaccine, because this virus will grow in the cooler, upper airway ys where it causes few symptoms and induces antibodies, but it will not grow in the warmer, lower airways where it can cause pneumonia -

MUTATIONS

Defective interfering particles.

- Some deletion mutants have the unusual property of being defective because they cannot replicate unless the deleted function is supplied by a “helper” virus.
- If they invade first and interfere with the necessary cellular processes, they also inhibit the development of typical viruses.
- Defective interfering particles may play a role in recovery from viral infection; they interfere with the production of progeny virus, thereby limiting the spread of the virus to other cells.
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INTERACTIONS BETWEEN VIRUSES

- **When two genetically distinct viruses infect a cell, three different phenomena can be observed.**
- **(1) Recombination**
- **is the transfer of genes across two chromosomes that is predicated on crossing over within regions of strong base sequence similarity. For viruses with double stranded DNA, recombination can be easily demonstrated.Recombination by**

RNA viruses rarely occurs .

Crossing over

Each diploid cell contains two copies of every chromosome, one derived from the maternal gamete and the other from the paternal gamete. These pairs of chromosomes, each derived from one parent, are called homologous chromosomes.

When diploid organisms undergo sexual reproduction, they first produce haploid gametes through meiosis. In prophase I of meiosis, homologous chromosomes connect with one another and exchange genetic material, resulting in some recombinant chromosomes. containing a mixture of genes derived from the maternal as well as the paternal chromosomes

INTERACTIONS BETWEEN VIRUSES

- **Reassortment is the term used when viruses with segmented genomes, such as influenza virus, exchange segments.**
- **This usually results in a much higher frequency of gene exchange than does recombination. Reassortment of influenza virus RNA segments causes major antigenic changes in the virus that are the basis for recurrent influenza epidemics.**

INTERACTIONS BETWEEN VIRUSES

(2) **Complementation**

- can occur when either one or both of the two viruses that infect the cell have a mutation that results in a nonfunctional protein (Figure 30–1). The nonmutated virus "complements" the mutated one by making a functional protein that serves for both viruses.
- Complementation is an important method by which a helper virus permits replication of a defective virus.
- One clinically important example of complementation is hepatitis B virus providing its surface antigen to hepatitis delta virus, which is defective in its ability to produce its own outer protein.
- This phenomenon is the basis for the complementation test, which can be used to determine how many genes exist in a viral genome.

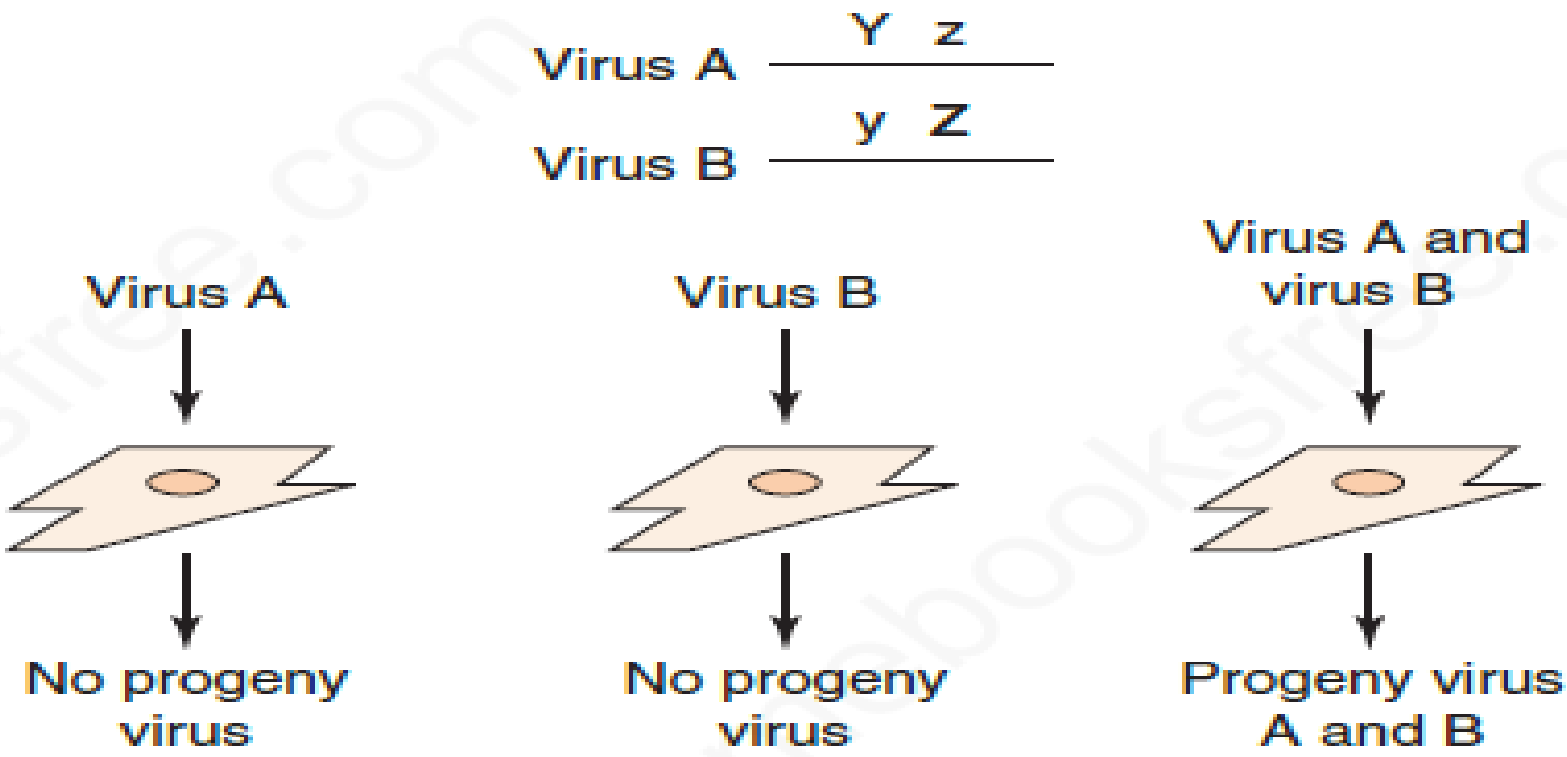

FIGURE 30–1 Complementation. If *either* virus A *or* virus B infects a cell, no virus is produced because each has a mutated gene. If *both* virus A and virus B infect a cell, the protein product of gene Y of virus A will complement virus B, the protein product of gene Z of virus B will complement virus A, and progeny of both virus A and virus B will be produced. Note that no recombination has occurred and that the virus A progeny will contain the mutated z gene and the virus B progeny will contain the mutant y gene. Y, Z, functional genes; y, z, mutated, nonfunctional genes.

INTERACTIONS BETWEEN VIRUSES

(3) In **phenotypic mixing**, the genome of virus type A can be coated with the surface proteins of virus type B (Figure 30–2). This phenotypically mixed virus can infect cells as determined by its type B protein coat. However, the progeny virus from this infection has a type A coat; it is encoded solely by its type A genetic material.

- An interesting example of phenotypic mixing is that of **pseudotypes**, which consist of the nucleocapsid of one virus and the envelope of another. Pseudotypes composed of the nucleocapsid of vesicular stomatitis virus (a rhabdovirus) and the envelope of human immunodeficiency virus (HIV; a retrovirus) are currently being used to study the immuneresponse to HIV

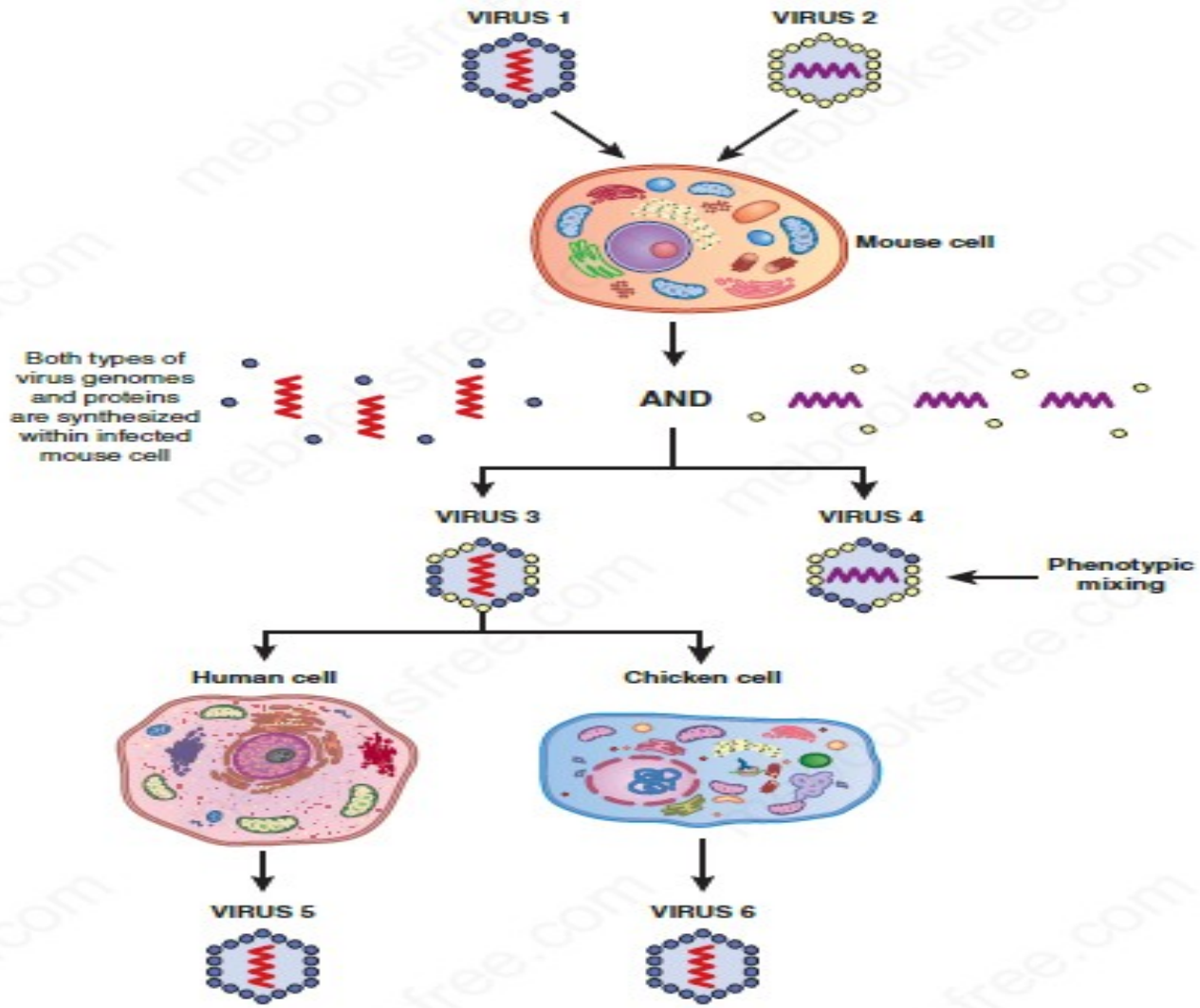

FIGURE 30–2 Phenotypic mixing. Initially, Virus 1 (Blue capsid proteins and vertical genome) and Virus 2 (Yellow capsid proteins and horizontal genome) infect the same mouse cell. Assume that Virus 1 can infect human cells but not chicken cells (a property determined by the blue surface proteins) and that Virus 2 can infect chicken cells but not human cells (a property determined by the yellow surface proteins). However, both Virus 1 and Virus 2 can infect a mouse cell. Within the mouse cell, both genomes are replicated and both blue and yellow capsid proteins are synthesized. As shown, some of the progeny virus (Viruses 3 and 4) exhibit *phenotypic mixing* because they have both the blue and the yellow surface proteins and therefore can infect both chicken cells and human cells. Note that in the next round of infection, when progeny Virus 3 infects either human cells or chicken cells, the progeny of that infection (Viruses 5 and 6) is determined by the vertical genome and will be identical to Virus 1 with only blue capsid proteins and a vertical genome. Similarly (but not shown), when progeny Virus 4 infects either human cells or chicken cells, the progeny of that infection is determined by the horizontal genome and will be identical to Virus 2. (Reproduced with permission from Joklik W et al. *Zinsser Microbiology*, 20th ed. Appleton & Lange, Norwalk, CT, 1992.)