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Stephen Harrison's Lecture Part 1:
Virus Structure: General Principles

Teaching Tools were prepared by Stephen Harrison.

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1. Keywords and Terms

Enveloped virus, non-enveloped virus, symmetry, virus assembly, molecular structure, membrane fusion, nucleic-acid packaging, viral entry

2. Lecture Notes

Viruses: definition and types

Questions to be discussed in this lecture

1. **Why do most non-enveloped viruses and a number of smaller enveloped viruses have symmetric structures?**
2. **What do the building blocks of these particles look like?**

3. **What do the proteins of some enveloped viruses look like?**

Principles: symmetry and genetic economy

1. **Definition of symmetry**
2. **Helical symmetry**
3. **Icosahedral symmetry**

Non-enveloped, icosahedrally symmetric shells: from simple to complex

1. **Parvoviruses: CPV**
   a. **Icosahedral symmetry characteristics**
   b. **Jelly-roll beta barrel of subunit**
   c. **Genome packaging capacity (ssDNA)**
2. **Picornaviruses**
   a. **Three distinct jelly-roll beta barrel subunits package plus-sense RNA**
   b. **Subunit arms help hold shell together**
   c. **Subunits processed from a polyprotein precursor, with myristoylated N-terminus**
3. **"T=3" shells: TBSV**
   a. **One kind of beta barrel in three distinct packing contexts**
   b. **Arms and hinges**
   c. **RNA packaging sequences (plus-sense)**
4. **Papillomaviruses**
   a. **dsDNA genome, minichromosome in all pentamer shell**
   b. **Role of adaptable, C-terminal "arms"**
   c. **A jelly-roll beta barrel packed slightly differently from the parvoviruses and plus-**
   d. **stranded RNA viruses just described**
5. **Adenoviruses**

Distinct subunit types for six-coordinated and five-coordinated positions

1. **Pentons have a single jelly-roll beta barrel with long projecting loops**
2. **Six-coordinated "hexons" are trimers, with two jelly-roll beta barrel domains**
3. **per subunit; very long outward-projecting loops (loops determine immune response**
4. **Structure held together by "cement" proteins, rather like arms of subunits in simpler viruses**

5. **Some bacteriophages have adenovirus-like organization**

Some general principles

1. **Defined subassemblies (e.g., hexon and penton of adenovirus; L1 penatmer of papillomavirus) permit efficient, "assembly-line" construction**
2. **Framework or scaffold (in simple cases, from subunit arms; in complex cases, from separate cement or scaffold proteins) ensures accurate assembly**
3. **Recurring assembly-unit architectural module: jelly-roll beta barrel**

A second recurring architectural module: the "HK97 fold" in double-strand DNA bacteriophages and herpresvirus capsids

Enveloped viruses: assembly by budding and entry by fusion

1. **Preassembly of internal structure vs. co-assembly of internal structure with envelope**
2. **Budding at cell surface and into intracellular compartments such as ER, Golgi**

Membrane fusion from cell surface or endosomal compartment during entry

Some examples of viral envelope proteins

Dengue virus: a compact icosahedral particle with a tightly organized membrane

1. **Envelope protein (E) mediates attachment and fusion**
2. **Fusion-promoting conformational change (dimer to trimer)**

Influenza virus hemagglutinin: spike-like structure for attachment and fusion

3. Recommended Reading

1. **Acheson, N. Fundmentals of Molecular Virology (2nd edition) John Wiley & Sons, Hoboken, NJ, 2011. Chapters 1-4.**
2. **Flint, S.J., Enquist, L.W., Racaniello, V.R., Skalka, A.M. Principles of Virology (3rd edition). ASM Press, Herndon, VA, 2008. Volume 1, Chapter 4.**

4. Review Questions

1. **Define symmetry of a three-dimensional object.**
2. **Describe icosahedral symmetry.**
3. **Why do the coats of virus particles have many copies of one or more simple building blocks (protein subunits)?**
4. **What feature of protein molecular architecture is present in all of the following virus particles: canine parvovirus, poliovirus, tomato bushy stunt virus, human papillomavirus, bacteriophage PRD1, human adenoviruses?**
5. **In papillomavirus and polyomavirus particles, what feature of the interactions between pentamers of the principal subunit is most important for allowing a pentamer to have six, specifically interacting neighbors.**
6. **How do most enveloped viruses acquire their lipid-bilayer membrane?**
7. **What is the common function of all fusion proteins (not just viral fusion proteins)?**
8. **What is a viral "fusion loop" or "fusion peptide"?**
9. **What do the fusion-promoting, conformational changes that dengue virus E protein and influenza virus undergo have in common?**

5. Answers to Review Questions

1. **Symmetry is the collection of operations (such as rotation) that bring the object into self-coincidence.**

2. **Icosahedral symmetry is a set of fivefold, threefold, and twofold rotation axes that together generate sets of 60 equivalent locations surrounding a central point.**
3. **Economy of coding information: viruses cannot package a large enough genome to encode many different coat proteins.**
4. **The jelly-roll beta barrel.**
5. **Protein "arms", extending from both the N- and C-terminal ends of the jelly-roll beta barrel domain of the protein subunit, mediate all of the pentamer-pentamer contacts. These arms can therefore shift direction, so that they can adjust to the different directions needed to contact their target subunit in another pentamer, while maintaining completely specific and invariant contacts within the target site itself.**
6. **By budding from the cytosol through a cellular membrane – either at the plasma membrane, leading to release of the completed particle in the extracellular space, or at an internal membrane, leading to release of the virion into the lumen of the internal organelle (e.g., ER, Golgi).**
7. **Accelerate (catalyse) the merging (fusion) of two lipid-bilayer membranes.**
8. **Hydrophobic segment(s) on the fusion protein that insert into the target-cell membrane at an intermediate stage in the fusion process, allowing the protein to link the target membrane and the viral membrane.**
9. **Large-scale structural rearrangements lead ultimately to a "postfusion" conformation in which the fusion peptide(s)/loop(s), inserted into the target membrane, and the transmembrane anchor, inserted across the viral membrane, have approached each other so closely that they force the two membranes together. In all known cases, the fusion-active form of the protein is a trimer, so that the final structure, once the two membranes have merged, is a trimer of hairpins.**

6. Discussion Questions

1. **Discuss the following aspects of genome packaging in viruses. Tight packing of nucleic acid or nucleoprotein within the virion. How tight? Are there examples of inefficient packing (i.e., empty spaces within the particle interior)?**
2. **What are the roles of "packaging sequence(s)" in viral genomes?**
3. **The capsid proteins of mammalian herpesviruses and those of many bacteriophages appear to have closely related structures. What implications might this observation**

have for the evolution of viruses? Certain cell-cell fusion proteins in various animal species (from C. elegans to humans) have structures (and probably corresponding mechanisms) that are extremely similar to those of some viral fusion proteins. How does this observation influence your thinking about viral evolution?

7. Answers to Discussion Questions

For answers, see Harrison, "Principles of Virus Structure", in Fields Virology, sixth edition, ed by D.M. Knipe and P.M. Howley, Lippincott, Williams & Wilkins, 2013.

8. Explain or Teach These Concepts to a Friend

1. **Enveloped and non-enveloped viruses: what is the distinction and how do these two structural categories correspond to distinct modes of assembly and cell entry?**
2. **Symmetry; icosahedral symmetry in particular, as an example.**

9. Research the Literature on Your Own

1. **Mechanism of packaging DNA into the heads of dsDNA bacteriophages.**
2. **Molecular architecture of viral fusion proteins.**