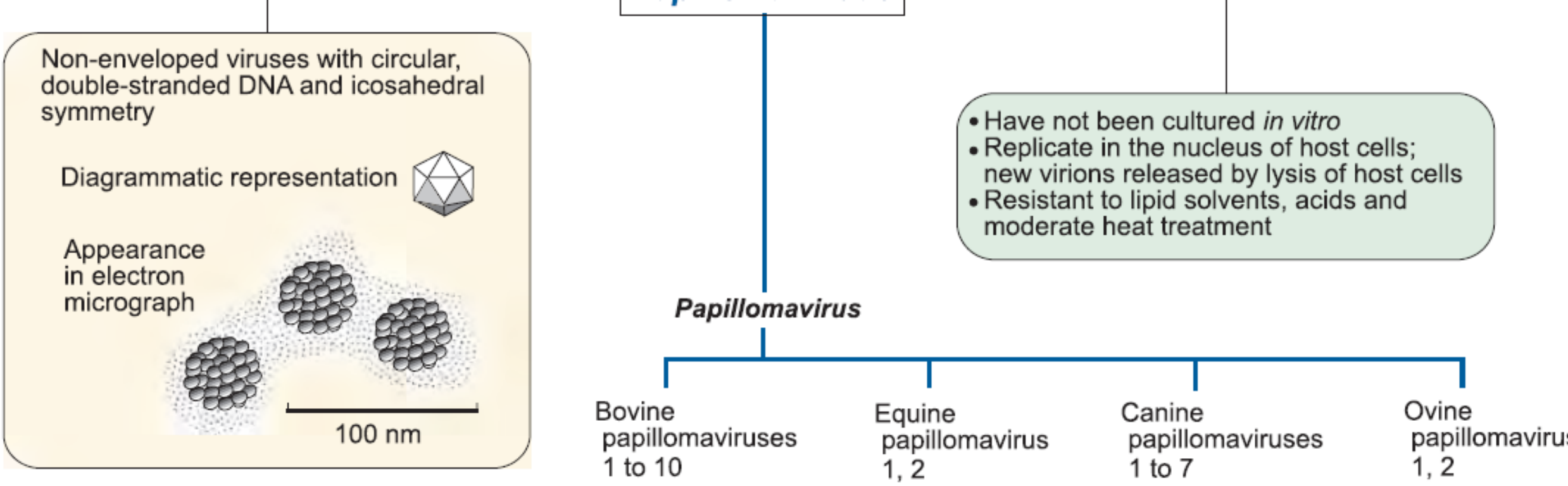
Papillomaviridae

Dr.Fawziah Ali



- Formerly, papillomaviruses were grouped with polyomaviruses in the family *Papovaviridae* . Infections with polyomaviruses are of minor veterinary importance, sometimes causing disease in psittacine birds and laboratory animals

- Some 30 genera are recognized in the family *Papillomaviridae* (Latin *papilla*, nipple, combined with Greek suffix -*oma* used to denote tumours). Non-enveloped, double-stranded DNA viruses with Icosahedral symmetry

Important Properties

- Papillomaviruses have doublestranded circular DNA and an icosahedral nucleocapsid.

- The early genes encode proteins involved in the synthesis of viral mRNA and in the replication of the progeny DNA genomes, and the late genes encode the structural proteins of the progeny virions.

- Two of the early genes, are implicated in carcinogenesis. They encode proteins that inactivate proteins encoded by tumor suppressor genes in host cells (e.g., the *p53* gene and the retinoblastoma [*RB*] gene,respectively). Inactivation of the p53 and RB proteins is an important step in the process by which a normal cell becomes a cancer cell.

- There are at least 100 types of papillomaviruses, classified primarily on the basis of DNA restriction fragment analysis. There is a pronounced **predilection of certain types to infect certain tissues**.

Summary of Replicative Cycle

- After attachment and uncoating, the genome DNA moves to the nucleus. Messenger RNA is synthesized by *host cell* RNA polymerase with early viral protein E2 acting as a transcriptional activator.

- Early viral protein E1 acts as a helicase that separates the DNA strands of the incoming viral genome. This allows the *host cell* DNA polymerase to synthesize the progeny DNA genomes.

- The initial progeny genomes are maintained as episomes in the nucleus. Most of the synthesis of progeny viral DNA occurs in conjunction with cellular DNA synthesis during S phase(**Synthesis Phase**).

- Late mRNA's encode both the major structural protein (L1) and the minor structural protein (L2). L1 protein comprises the capsid of PV virions. L1 has the ability to self assemble into capsids *in vitro* and it is this form that is the immunogen in the HPV vaccine.

- L2 protein aids in the packaging of genome DNA into the progeny virions as well as in uncoating the genome when they infect the next cell.

- The PV infects the cells of the skin's basal layer at first, but the basal cells do not produce any virus. Infectious virions are instead formed by squamous cells on the surface, which increases the chances of efficient transmission.

- In malignant cells, viral DNA is integrated into host cell DNA in the vicinity of cellular proto-oncogenes, and *E6* and *E7* are overexpressed . However, in latently infected, nonmalignant cells, the viral DNA is episomal, and *E6* and *E7* are not overexpressed. This difference occurs because another early gene, *E2*, controls *E6* and *E7* expression. The *E2* gene is functional when the viral DNA is episomal but is inactivated when it is integrated

Pathogenesis & Immunity

- Papillomaviruses infect squamous epithelial cells and induce within those cells a characteristic perinuclear cytoplasmic vacuole. These vacuolated cells, called **koilocytes,**are the hallmark of infection by these viruses (Figure 38–2).

- Most warts are benign and do not progress to malignancy.However the proteins encoded by viral genes *E6* and *E7* interfere with the growth-inhibitory activity of the proteins encoded by the *p53* and *RB* tumor suppressor genes and thereby contribute to oncogenesis by these viruses.

- Both cell-mediated immunity and antibody are induced by viral infection and are involved in the spontaneous regression of warts.

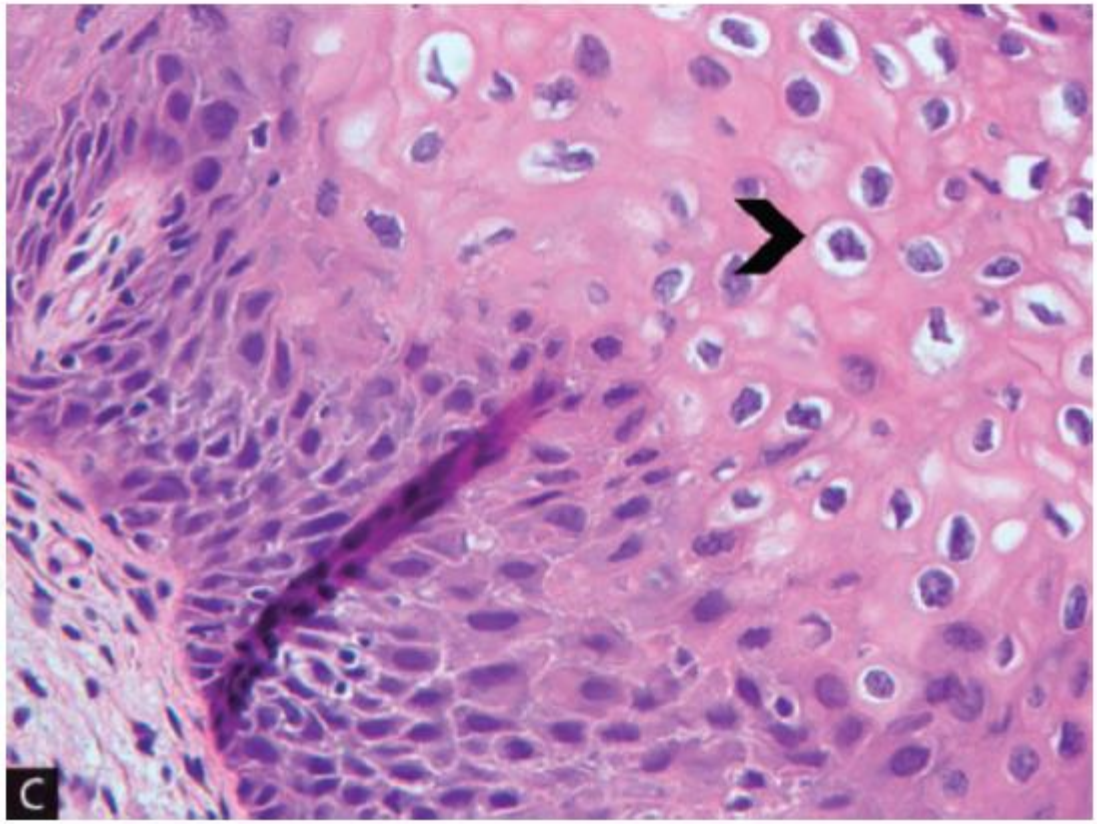


FIGURE 38–2 Koilocytes. The black arrowhead points to a koilocyte, seen here in a biopsy specimen of cervical intraepithelial neoplasia caused by human papilloma virus. Koilocytes have a small condensed nucleus and a large perinuclear cytoplasmis vacuole. 400X magnification. (Reproduced with permission from Kemp, WL, Burns, DK and Brown TG. *Pathology: The Big picture.* 2008. Copyright © 2008 by The McGraw-Hill Compa

Laboratory Diagnosis

- Infections are usually diagnosed clinically. The presence of koilocytes in the lesions indicates PV infection.

- A polymerase chain reaction (PCR)–based test can be used to detect the presence of the DNA of PV

- Diagnostic tests based on detection of antibodies in serum or on isolation of the virus from a tissue are not used.

Clinical infections

- Each papillomavirus tends to be host-specific and to produce proliferative lesions in specific anatomical sites.

- Although infections with papillomaviruses occur in many animal species, only those which affect cattle, horses and dogs are of clinical significance.

- The epitheliotropic, host-specific papillomaviruses cause proliferative lesions (warts) in many mammalian and avian species.

- The DNA sequences of numerous papillomaviruses have been identified, allowing for specific detection in lesions despite the fact that they have not been grown in cell culture.

- In infected cells, the viral DNA is usually episomal(Episomes, in eukaryotes, are extrachromosomal, closed circular DNA molecules of a plasmid or a viral genome origin, that are replicated autonomously in the host cell and therefore, they bear significant vector potential for the transfer of nucleic acids into cells.).

- Papillomaviruses are used experimentally for inserting foreign DNA into cultured cells.

- Finger-like extensions of proliferating epithelium are supported by a narrow center of mature fibrous tissue in typical papillomas.

- The fibrous tissue component predominates in fibropapillomas.

- In some host species,several types of papillomaviruses can cause neoplastic change. Progression of papillomas to Malignant tumours has been documented in humans, cattle and rabbits.

- Malignant transformation of alimentary and urinary tract papillomas may occur in cattle ingesting bracken

Table 55.1 Papillomaviruses of domestic animals and associated clinical conditions.

Virus	Clinical conditions
Bovine papillomavirus	
Types 1 and 2	Fibropapillomas in young cattle; occur mainly on the head and neck and occasionally on the penis. Implicated in the pathogenesis of equine sarcoids. Type 2 is implicated in bladder neoplasia and enzootic haematuria
Type 3	Cutaneous papillomas with a tendency to persist
Type 4	Papillomas in the alimentary tract; malignant transformation may result from ingestion of bracken fern
Type 5	Fibropapillomas on the teats ('rice grain' type)
Type 6	Papillomas on the teats ('frond' type)
Equine papillomavirus	Papillomas in young horses; occur mainly around lips and on nose
Canine oral papillomavirus	Irregularly-shaped papillomas in the oral cavity of young dogs
Ovine papillomavirus	Papillomas and fibropapillomas (rare)

Pathogenesis

- Papillomaviruses usually infect the basal cells of squamous epithelium as a result of minute abrasions.

- They may also gain entry at vulnerable sites such as junctions between different types of epithelia.

- Infected cells proliferate and differentiation is delayed. Viral gene expression is restricted during this proliferative phase.

- Full gene expression results in the production of viral capsids only after cellular differentiation begins in the upper layers of the epithelium.

- New virions can be visualized by electron microscopy in the nuclei of differentiated keratinized cells. The release of virus occurs during desquamation of infected cells from the surface of lesions.

Diagnosis

The clinical appearance of papillomas (warts) is distinctive. Laboratory confirmation is not usually required for papillomatous lesions.

Histopathological examination may be required to determine the nature of some lesions, especially equine sarcoids.

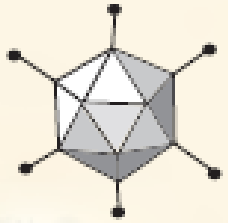
Electron microscopic examination of specimens from the epidermis may reveal characteristic virus particles.

Hybridization assays and PCR methods are available for the detection of papillomavirus DNA, but are not used routinely. Isolates can be typed by extraction of DNA and restriction endonuclease analysis or by Southern blotting

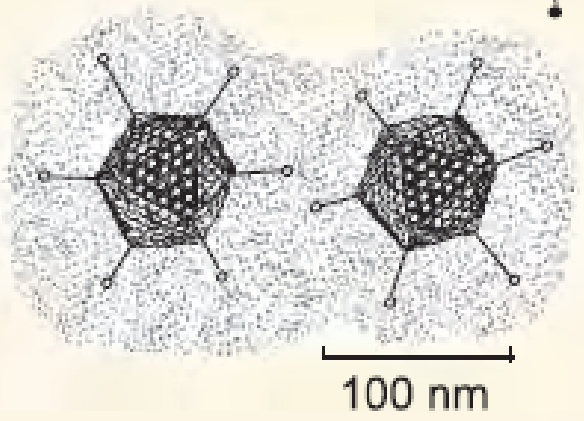
Adenoviridae

Non-enveloped, double-stranded DNA viruses with icosahedral symmetry

Diagrammatic representation



Appearance in electron micrograph



- Replicate in nuclei, forming intranuclear inclusion bodies
- Moderately stable in the enviro

Aviadenovirus

Fowl adenovirus A,B,C,D,E
Goose adenovirus
Turkey adenovirus
Falcon adenovirus

Mastadenovirus

Bovine adenovirus A,B,C
Canine adenovirus 1, 2
Equine adenovirus A,B
Ovine adenovirus A,B
Porcine adenovirus A,B,C

Atadenovirus

Duck adenovirus A
Ovine adenovirus D
Bovine adenovirus D

Siadenoviru

Frog adenovirus
Turkey adenovir

Important Properties

- Adenoviruses have linear DNA and an **icosahedral** nucleocapsid.
- They are the only viruses with a **fiber** protruding from each of the 12 vertices of the capsid.
- The fiber is the organ of attachment and is a hemagglutinin. When purified free of virions, the fiber is toxic to host cells.
- Tissue cultures of human adenoids were the first source of adenoviruses (Greek adenos, gland).
- These non-enveloped, double-stranded DNA viruses comprise five genera: *Mastadenovirus*(mammalian adenoviruses), *Aviadenovirus* (avian adenoviruses), *Atadenovirus* (viruses of vertebrates), *Siadenovirus* (amphibian and avian viruses) and *Ichtadenovirus* (fish adenoviruses).
- Serogroups and serotypes are based on neutralization assays.

Summary of Replicative Cycle

- After attachment to the cell surface via its fiber, the virus penetrates and uncoats, and the viral DNA moves to the nucleus.

- Host cell DNA-dependent RNA polymerase transcribes the early genes, and splicing enzymes remove the RNA representing the introns, resulting in functional mRNA.

- Early mRNA is translated into nonstructural proteins in the cytoplasm. After viral DNA replication in the nucleus, late mRNA is transcribed and then translated into structural virion proteins. Viral assembly occurs in the nucleus, and the virus is released by lysis of the cell, not bybudding.

Pathogenesis & Immunity

Adenoviruses infect the mucosal epithelium of several organs (e.g., the **respiratory tract** [both upper and lower],the **gastrointestinal tract,** and the **conjunctivas**).

Immunity based on neutralizing antibody is type-specific and lifelong.

- In addition to acute infection leading to death of the cells, adenoviruses cause a latent infection, particularly in the adenoidal and tonsillar tissues of the throat.

Clinical infections

- Adenoviruses have a natural host range generally confined to a single species or to closely related species.
- Infection is commonin animals and humans.
- Adenovirus infections can be particularly severe in dogs and domestic fowl.
- In most domestic mammals, adenovirus infections are associated occasionally with enteric or respiratory problems.

Table 56.1 Adenoviruses of veterinary importance.

Virus	Comments
Canine adenovirus	Two strains are recognized, canine adenovirus (CAV)-1 and CAV-2. CAV-1 causes infectious canine hepatitis, with lesions arising from direct cytopathic effects and immune complex formation. CAV-2 is involved in infectious tracheobronchitis (kennel cough), a highly contagious respiratory disease
Equine adenovirus A	Usually a subclinical or mild respiratory infection in the horse population. In Arabian foals with severe combined immunodeficiency disease, associated with pneumonia, which is invariably fatal
Bovine adenoviruses	Associated with occasional outbreaks of respiratory and enteric disease
Ovine adenoviruses	Associated with occasional outbreaks of respiratory and enteric disease
Porcine adenoviruses	Usually subclinical infections; occasionally cause diarrhoea
Fowl adenoviruses	Frequently isolated from healthy birds or following respiratory disease. Associated with quail bronchitis, inclusion body hepatitis and hepatitis–hydropericardium syndrome
Duck adenovirus A	Causes egg drop syndrome in laying hens
Turkey adenovirus A	Causes turkey haemorrhagic enteritis (dysentery in 4 to 12-week-old poults with mortality rate of up to 60%) and marble spleen disease in pheasants (characterized by sudden death, pulmonary oedema and splenic necrosis in 2 to 8-month-old birds)

- Avian adenoviruses occur worldwide in a wide range of species. Infection is extremely common in poultry flocks.

- Most of these infections are either subclinical or associated with relatively mild disease. However, severe disease may follow infection with duck adenovirus A(egg-drop syndrome) and turkey adenovirus A (haemorrhagic enteritis).

Laboratory Diagnosis

The most frequent methods of diagnosis are isolation of the virus in cell culture and detection of a fourfold or greater rise in antibody titer.

Complement fixation and hemagglutination inhibition are the most important serologic tests.PCR is also can be used