PAPILLOMAVIRIDAE

(Latin, papilla; nipple – oma; tumor)

Classification

The family "*papillomaviridae*" consists of following genus;

Genus	Members
Papillomavirus	Bovine papillomavirus
	Ovine papillomavirus
	Canine papillomavirus
	Rabbit papillomavirus

General Properties

- Papillomaviruses are non-enveloped, double stranded DNA viruses.
- The viral capsid is composed with 72 capsomers of tubular and other aberrant forms.
- The nucleocapsid has an icosahedral symmetry.

Physiochemical Properties

- Papillomaviruses are thermostable and withstand heating for 30 min at 56-65 C
- The viruses are acid stable and resistant to lipid solvents.

Cultivation and Growth Properties

- The viruses have limited cell tropism and difficult to grow in cell cultures.
- Although the viruses do not replicate in vitro, but most of the viruses can transform cells.
- There is no integration of the viral DNA into the cellular DNA.
- The transformed cells contain viral proteins in the plasma membrane, but no infectious virus is present in transformed cells.

Host Susceptibility

- Varieties of animal species such as cattle (bovine papillomas), horse (Equine papillomas & Equine sarcoids), sheep, pig, dog (Canine oral papilloma), and rabbit (cotton tail rabbit disease) are susceptible to papillomavirus infection.

Pathogenesis

- Entry of viruses commonly occurs through *abrasions of the skin*.
- The virus multiplication takes place in the nucleus of the host's cell.
- The viruses have the affinity for epithelial cells mainly squamous epithelial cells of skin and upper alimentary tract.
- The incubation period between virus infection & papilloma development is 3-18 months.
- Papillomas vary in size (small nodule to large cauliflower like growth).

Immunity

- Most papillomas in animals are *self-replicating* and spontaneous regression of fibro-papillomas usually occurs within 4-6 months.
- Development of antibodies 2-3 weeks after infection with bovine papillomaviruses has been observed.

Diagnosis

- Gross lesions, Negative stain EM is useful to demonstrate the virus in tumor tissue homogenates.
- Serological tests: RIA, ELISA, and HI have been used successfully.

- The reliable and rapid diagnostic method for bovine papillomavirus is "immunoperoxidase" staining of paraffin embedded tissue sections.

Prevention and Control

- Autongenous vaccines containing homogenized tumor tissues inactivated with formaldehyde have been used little success.
- Genetically engineered vaccines developed for the bovine papillomavirus reported useful.
- Efforts should be made to maintain clean herds.

POLYOMAVIRIDAE

(Latin, poly; many – oma; tumor)

The family "*polyomaviridea*" includes only one genus;

Genus	Members
Polyomavirus	Bovine polyomavirus
	Murine polyomavirus
	SV-40 (monkey virus)

General Properties

- Polyomaviruses resemble the papillomaviruses.
- The viruses are non-enveloped, the genome contains double strand circular DNA.
- The nucleocapsid has icosahedral symmetry.
- Three capsid proteins (VP_1, VP_2, and VP_3) and several small basic proteins (T, t) are associated with the viral DNA replication.

Cultivation and Growth Properties

- Polyomaviruses grow in primary and secondary cultures of mouse, rat and hamsters.
- They multiply in mouse embryo and mouse kidney cells and give rise to cell death and plaque formation.

Host Susceptibility

- Rodents particularly mice, hamsters and rats (tumor formation), monkeys [Simian vacoulating virus $_{40}$ (SV_{40} virus)] and man are susceptible.
- Monkeys with SV_{40} are carrier, but show no symptoms.

Pathogenesis:

- Rarely produce clinical disease (tumor) in natural host(rodents) because the concentration of viruses in secretions and excretions of naturally infected rodents is insufficient to induce tumor formation.
- Parotid tumors are the most frequent in mice and sarcomas in hamsters.
- Experimentally when large amounts of virus are injected into neonatal rodents → may die of infections of kidney, salivary gland, thyroid and other organs.
- Histologically, diverse tumors (*polyomas*) can be seen in the organ.

Cultivation

- Polyomaviruses grow in primary and secondary cultures of mouse, rats, and hamster cells. They multiply and give rise to cell death and plaque formation.
- Many polyomaviruses are oncogenic in the lab system and have never been shown to be so in the world.

HEPADNAVIRIDAE

Classification

The family includes two genera as follows;

Genus	Members
Orthohepadnavirus	Hepatitis B virus of man
Avihepadnavirus	Duck hepatitis B virus

General Properties

- Members of this family are enveloped viruses with icosahedral symmetry.
- Their genome is double stranded DNA and single stranded DNA. DNA/RNA hybrid.
- Genome encodes genes of 4 proteins; in which 2 are surface & core proteins.
- Third (3^{rd}) one is DNA polymerase and 4^{th} one is unknown.
- Viral DNA polymerase acts as a reverse transcriptase thus virus is also known as "DNA Reverse transcribing virus".

Replication

- The replication of viruses is unique.
- The *first step* in replication is the conversion of the asymmetric DNA to covalently closed circle DNA.
- The *second step* involves the transcription of the closed circle DNA by host transcriptase to generate an RNA template (the *pregenome*).
- The *third step* involves the synthesis of the first minus-stranded DNA by copying the pregenomic RNA by the reverse transcriptase.
- *Finally*, the synthesis of the second plus stranded DNA occurs by copying the first DNA strand using an oligomer of viral DNA as primer.

DUCK HEPATITIS B VIRUS

The duck hepatitis B virus can replicate in liver, pancreas, kidney and spleen and is transmitted almost exclusively by the vertical roué, whereas the mammalian hepadnaviruses are passed primarily by horizontal spread and infect only the liver.

PRIONS

(Unconventional Slow Viruses)

A prion is a small proteinacious infectious particle that appears to be a modified host protein. It is filterable and it can transmit the disease. Unlike conventional viruses, these agents have no virion structure or genome, elicit no immune response, and are extremely resistant to inactivation by heat, disinfectants, and radiation.

Table: 1 Comparison of Classic Viruses and Prions

Characteristic	***Virus***	***Prion***	***Viroid***
Filterable infectious agent	Yes	Yes	Yes
Presence of nucleic acid	Yes	No	Yes (ssRNA)
Presence of protein	Yes	Yes	No
Defined morphology (by EM)	Yes	No	No
Disinfection by:			
Formaldehyde	Yes	No	No
Protease	Some	No	No

Heat (80^0C)	Most	No	-
Ionizing and UV radiation	Yes	No	-

Disease

Cytopathic effect (in vitro)	Yes	No	Plant pathogens and also causing Hepatitis D
Incubation period	Variable	Long	
Immune response	Yes	No	
Interferon production	Yes	No	
Inflammatory response	Yes	No	

Resistance:

For GSS and CJD, neurological tools and electrodes should be disinfected in 5% hypochlorite solution or 0.1M NaOH or autoclaved at 15psi for 1 hour.

Slow virus/Prion Diseases

Human	Kuru
	Creutzfeldt – Jakob disease (CJD)
	Gerstmann – Straussler – Scheinker disease (GSS disease)
	Fetal familial insomnia (FFI)
Animal	Scrapie (sheep and goats)
	Transmissible mink encephalopathy
	Bovine spongiform encephalopathy (Mad cow disease)
	Chronic wasting disease (mule, deer, and elk)

Pathogenic Characteristics of Prions

- No Cytopathogenic effect in vitro.
- Long doubling time of at least 5.2 days
- Long incubation period (1-3 years)
- Cause vaculation of neurons (spongiform), Amyloid-like plaque and gliosis.
- Symptoms that include loss of muscle control, shivering, tremors, dementia.
- Lack of antigenicity
- Lack of inflammation
- Lack of immune response
- Lack of interferon production.

Structure and Physiology of Prions

Like viruses, the prions can pass through filters that block the passage of particles more than 100nm and still transmit disease. Unlike viruses, the agents are resistant to a wide range of chemicals and physical agents such as formaldehyde, UV radiation and heat to 80 C.

The prototype of these agents is ‘scrapie – infected hamsters have scrapie-associated fibrils in their brains. These fibrils are infection and contain PRION.

The prion, which lacks detectable nucleic acids, consists of aggregates of protease – resistant, hydrophobic glycoproteins, which for ‘scrapie’ is termed P^rP^{sc} (Scarpie prion protein) which is 27000-3000 Da. Human and other animals encode a protein PrPc (Cellular prion protein) in its protein sequence but differs in many other properties. (Table: 2)

Comparison of Scrapie prion protein (PrPsc) and Cellular prion protein (PrPc)

		P^rP^{sc}	P^rP^c
1.	Structure	Globular	Extended
2.	Protease resistance	+	--
3.	Presence in srapie fibrils	+	--
4.	Location in or on cells	Cytoplasmic vesicles	Plasma membrane
5.	Turnover	Days	Hours

Association of Prions with Clinical Syndromes

These agents cause a progressive, degenerative neurologic disease with a long incubation period but with rapid progression to death after the onset of symptoms. The progression of transmissible Creutzfeldt-Jacob disease (CJD) is as follow;

Clinical Symptoms

The spongiform encephalopathies are characterized by a loss of muscle control, shivering, myoclonic jerks and tremors, loss of coordination, rapidly progressive dementia and death.

Pathogenesis

Spongiform encephalopathy describes the appearance of the vacuolated neurons as well as their loss of function and the lack of an immune response or inflammation. Vacuolation of the neurons, the formation of Amyloid-containing plaques and fibrils, a proliferation and hypertrophy of ostrocytes and the fusion of neurons and adjacent glial cells are observed.

The PrPsc is taken up by the neurons and phagocytic cells but is difficult to degrade a feature that may contribute to the vacuolation of the brain tissue. In addition, prions reach high concentrations in the brain, further contributing to the tissue damage.

Prions can also be isolated from tissues other than brain, but only the brain shows any disease. No inflammation/immune response to the agent is generated, distinguishing the disease from classical viral encephalitis. A protein marker (14-3-3 brain protein) can be detected in the cerebrospinal fluids of symptomatic individuals.

The incubation periods for CJD and kuru may be as long as 30 years, but one symptoms become evident, the patient dies within a year.

Epidemiology:

CJD (***Creutzfeldt Jacob disease***)

Transmission can occur by: i) Ingestion ii) Transplantation of contaminated tissue (e.g. corneas) iii) contact with contaminated medical devices (e.g. brain electrodes) and iv) food.

CJD, FFI (fetal familial insomnia) and GSS diseases are inheritable, and families with genetic histories of these diseases have been identifies. These diseases are rare but occur world-wide.

KURU

It may be characterized by shivering and trembling condition; was limited to a very small area of the New Guinea highland. The disease was related to the cannibalism practices of the Fort tribe of New guinea. Cessation of this cannibalism custom has been stopped the spread of kuru.

Laboratory Diagnosis

1. There are no methods for direct detection of these agenst via EM, antigen detection or nucleic acid probes.
2. No serological test can detect antibody.
3. The diagnosis is made on clinical grounds, with conformation by the characteristic histological changes brow tissue.
4. Demonstration of proteinase K –resistant from PrP in western blot using antibody to PrP can conform a case of CJD.

Treatments, Prevention/Control

- No treatment exists for Kuru or CJD.
- Disinfect instruments before reused by using autoclave.

GENERAL AND SYSTEMIC VIROLOGY
(MICRO – 303)

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POLYOMAVIRIDAE

HEPADNAVIRIDAE

PRIONS

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