Unit 1.4 Sub Viral entities: viroids, virusoids, prions

- **Viroids** are infectious agents that consist only of RNA.
- **Virusoids** formerly called **satellite RNAs**, similar to viroids in that they also consist of RNA.
- **Prions** are infectious agents that consists only of protein

No.	Viroids	Virusoids
1	Covalently closed, circular, ssRNAs	Covalently closed, circular, ssRNAs with regions capable of intrastrand base pairing
2	About **250 to 370** nucleotides long	They encode one or more gene products
3	Circular RNA normally exists as a rodlike shape due to intrastrand base pairing, which forms double stranded regions with single stranded loops	Typically need a helper virus in order to infect host cells
4	Some viroids found in the nucleolus of infected host cells, where between 200-10,000 copies may be present	Helper virus supplies gene products and other materials needed by the virusoid for completion of its replication cycle
5	Others are located within chloroplasts	
6	RNA of viroids does not encode any gene products, so they cannot replicate themselves.	They encode one or more gene products and they typically need a helper virus in order to infect host cells.
7	Viroid is replicated by one of the host cell's DNA-dependent RNA polymerases, host polymerase uses the viroid RNA as template for RNA synthesis, rather than host DNA	Best studied virusoid is **human hepatitis D virusoid**, 1700 nucleotides long Uses the hepatitis B virus and the hepatitis D virusoid, the virusoid RNA and its gene product called **delta antigen** can be packaged within the envelope of virus
8	Host polymerase synthesizes a complementary RNA molecule, a negative strand RNA, this then serves as the template for the same host polymerase and new viroid RNAs are synthesized. Both steps occur by rolling-circle mechanisms	Enveloped virusoids and delta antigens are capable of entering other host cells, where the virusoid RNA is transcribed by the host's RNA polymerase II

Viroids

- Viroids cause over 20 different plant diseases, including potato spindle-tuber disease, exocortis disease of citrus trees and chrysanthemum stunt disease.
- Plant may be infected with a viroid without showing symptoms – that is, it may have latent infection.

- However, the same viroid in another host species may cause severe disease.
- The pathogenicity of viroids is not well understood, but it is known that particular regions of the RNA are required as removal of this region blocks the development of disease.
- Viroids cause disease by triggering a eukaryotic response called **RNA silencing,** which normally functions to protect against infection by dsRNA viruses.
- During RNA silencing, the cell detects the presence of dsRNA and selectively degrades it. Viroids may use this response by hybridizing to specific host mRNA molecules to which they have a complementary nucleotide sequence.
- Formation of the hybrid **viroid:host mRNA** double-stranded molecule is thought to elicit RNA silencing.
- This results in destruction of the host message and therefore silencing of the host gene. Failure to express a required host gene leads to disease in the host plant.
- Potato spindle-tuber viroid (PSTV) is the most intensely studied viroid. Its RNA consists of about 359 nucleotides, much smaller than any virus genome.
- Several PSTV strains have been isolated ranging in virulence from those that cause only mild symptoms to lethal varieties.
- All variations in pathogenicity are due to few nucleotide changes in two short regions on the viroid. It is believed that these sequence changes alter the shape of the rod and thus its ability to cause disease.

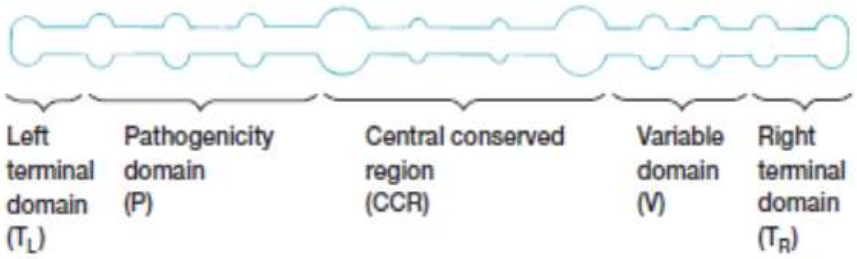
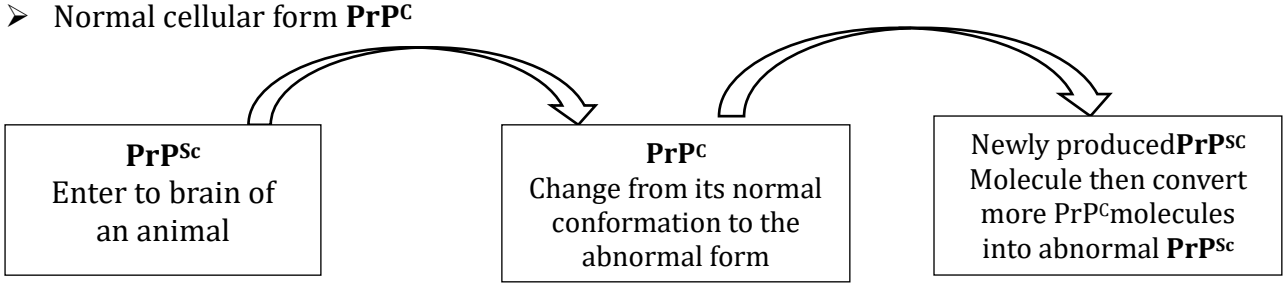


Fig.: Viroid structure

Prions

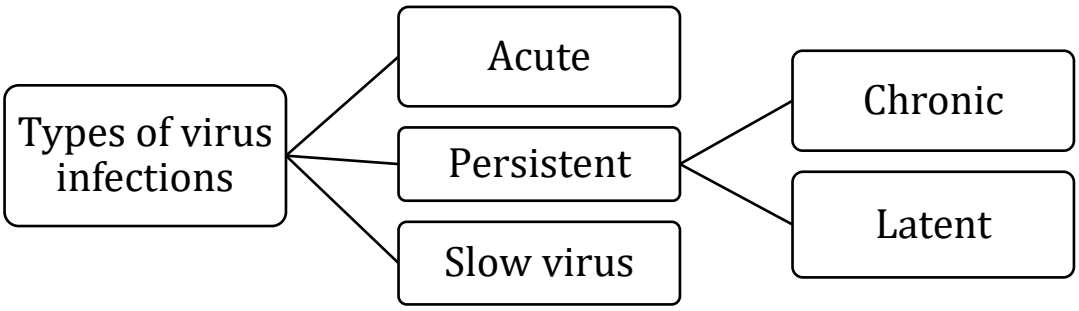
- Prions (for proteinaceous infectious particle) cause a variety of neurodegenerative diseases in humans and animals.
- The best-studied prion is the scrapie prion, which causes the scrapie in sheep.
- Afflicted animals lose coordination of their movements, tend to scrape or rub their skin, and eventually cannot walk.
- Scrapie is caused by an abnormal form of a cellular protein.
- Abnormal form **PrP^{Sc}**(Scrapie-associated prion protein)
- Normal cellular form **PrP^{C}**



- **PrP^{Sc}**causes conformational changes. The following supported model
  1. **PrP^{Sc}**directly interacts with PrP^{C}causing the change.
  2. **PrP^{Sc}**causes PrP^{C} to fold abnormally how this triggers neuron loss is poorly understood.
  3. Interaction of **PrP^{Sc}** with PrP^{C} serves to cross-link PrP^{C} molecules. The cross-linked PrP^{C} molecules trigger a series of events called apoptosis or programmed cell death.
- Thus, the normal, but cross-linked, protein causes neuron loss, whereas the abnormal protein acts as the infectious agent.
- In addition to scrapie, prions are responsible for
- 1. Bovine spongiform encephalopathy (BSE or "mad cow disease")
- 2. Human diseases kuru
- 3. Fatal familial insomnia,
- 4. Creutzfeldt-Jakob disease (CJD) and
- 5. Gerstmann-Strassler-Scheinker syndrome (GSS).
- All result in progressive degeneration of the brain and eventual death.
- At present, there is no effective treatment.
- Variant CJD differs from CJD in origin only, people acquire vCJD by eating contaminated meat, while CJD is an extremely rare condition caused by spontaneous mutation of the gene that encodes the prion protein.
- CJD and GSS are rate and cosmopolitan in distribution among middle-aged people, while kuru has been found only in the Fore, an eastern New Guinea tribe.
- This tribe had a custom of consuming dead kinsmen.
- Women and children were given less desirable body parts to eat; this included the brain.
- Thus they and their children were infected.
- Cannibalism was stopped many years ago, and kuru has been eliminated.

Types of Virus infections: Persistent, Latent and Slow virus infections

- Times and duration of viral infection depends on the type of virus and host.
- Following are different types of virus infections



1. **Acute Infections:**

- This type of infections have rapid onset and last for a relatively short time.

2. **Persistent Infections:**

- This infection last for many years.
- There are several kinds of persistent infections

2a. Chronic virus infections: virus is almost **always detectable** and clinical symptoms may be either **mild or absent** for long periods.

- **Examples –** Hepatitis B virus and HIV

2b. Latent virus infections: The virus stops reproducing and remains dormant for a period for long time until its activation.

- During latency, no symptoms or viruses are detectable, although antibodies to the virus may be present at low levels.
- **Examples:**
  1. Herpes simplex virus
  2. Varicella-zoster virus (Chicken pox)
  3. Cytomegalovirus
  4. Epstein-Barr Virus (Mononucleosis)
- Causes of Persistence and latency are multiple, although the precise mechanisms are still unclear.
  - Virus genome may be integrated into the host genome thereby becoming a **provirus**.
  - Viruses may become less antigenic and thus less susceptible to attack by the immune system. Often virus infections are latent in a site not subject to immune attack, such as the central nervous system.
  - Viruses may also mutate to less virulent and slower reproducing forms. Sometimes a deletion mutation produces a **defective interfering (DI) particle** that cannot reproduce but slows normal virus reproduction, thereby reducing host damage and establishes a chronic infection.

3. **Slow virus diseases:**

- A small group of viruses causes extremely slowly developing infections, often called **slow virus diseases** or **slow infections**.

- In this type of infections symptoms may take years to emerge.
- Example: Measles virus occasionally produces a slow infection.
- A child may have a normal case of measles, then 5 to 12 years later develop a degenerative brain disease called **S**ubacute **S**clerosing **P**anencephalitis (SSPE).
- Lentiviruses such as HIV also cause slow disease.

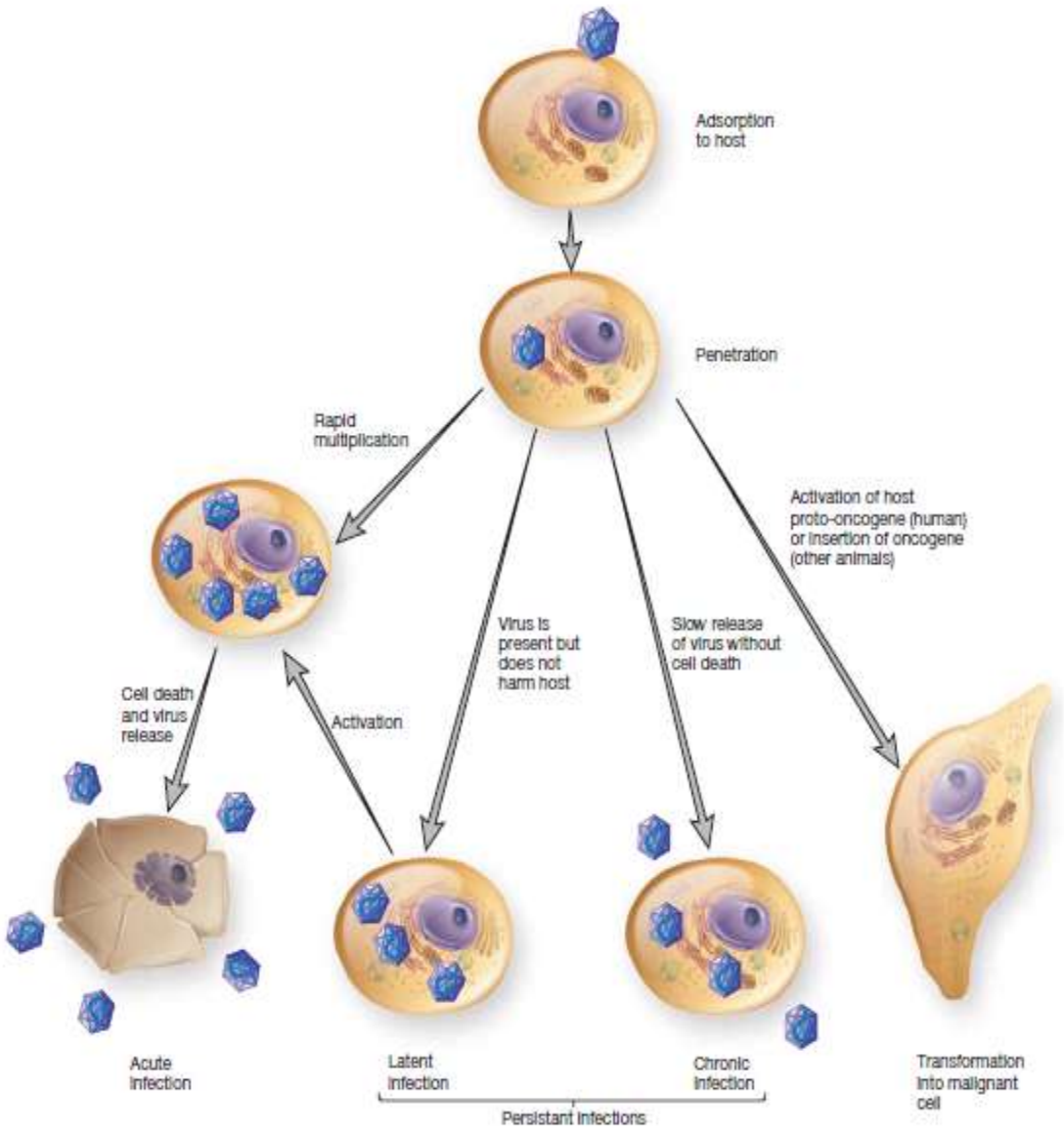


Figure 18.13 Types of Infections and Their Effects on Host Cells.

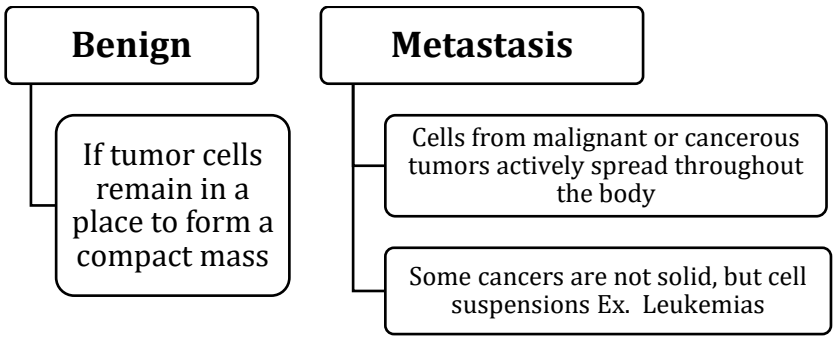
Fig.: Types of viral infections (Ref: Microbiology by. Prescott, Harley, & Kleins 7th edition)

ONCOGENIC VIRUSES

- **Cancer** word derived from Latin cancer, crab. It is one of the most serious medical problems in developed nations.
- **Tumor** derived from Latin word tumere means to swell. It is a growth or lump of tissue resulting from **neoplasia**, abnormal new cell growth and reproduction due to loss of regulation.
- Tumor cells have aberrant shapes and altered plasma membranes that may contain distinctive tumor antigens.
- Their unregulated proliferation and loss of differentiation result in invasive growth that forms unorganized cell masses. This reversion to a more primitive or less differentiated state is called **Anaplasia**.

Types of tumors

- There are two major types of tumors with respect to overall form or growth pattern.



- Cancer is multi-factorial includes, age, diet, lifestyle, cigarette smoke, alcohol, hereditary, tobacco, chemicals, viruses etc.
- Carcinogenesis is a complex, multistep process.
- Cancer-causing genes or oncogenes, are directly involved.
- Origin of oncogenes: 1. some oncogenes are contributed to a cell by viruses. 2. Others arise from genes within cell called proto-oncogenes.
- Proto-oncogenes are cellular genes required for normal growth. If **mutated or over expressed** they may become oncogenes.
- Their products contribute to the malignant transformation of the cell.
- Many oncogenes are involved in the regulation of the cell growth and signal transduction. For ex. Some code for growth factors that regulate cell reproduction.
- Chances of developing cancer rise with age because an older person will have had a longer time to accumulate the mutations needed for oncogenic transformation. Immune surveillance and destruction of cancer cells also may be less effective in older people.
- Virus particle and components within tumor cells, using techniques such as electron microscopy, immunologic tests, DNA-based assays, and enzyme assays.

- Attempts can also be made to isolate suspected cancer viruses by cultivation in tissue culture or other animals. Sometimes a good correlation between the presence of a virus and cancer can be detected.
- At present, following viruses have been implicated in the genesis of at least eight human cancers. With the exception of a few retroviruses, these viruses have dsDNA genomes.

No.	Virus name	Type of Cancer
1	Epstein-Barr Virus (EBV)	1. Burkitt's lymphoma malignant tumor of the jaw and abdomen in children of Africa 2. Nasopharyngeal carcinoma
2	Hepatitis B virus	Liver cancer (hepatocellular carcinoma)
3	Hepatitis C virus	Cirrhosis of liver lead to liver cancer
4	Human Herpes virus 8 and HIV	Kaposi's sarcoma
5	Human Papillomavirus	Cervical cancer
6	Human T-cell lymphotropic virus HTLV-1 HTLV-2	1. Adult T-cell leukemia 2. Hairy cell leukemia respectively

- Viruses known to cause cancer are called **ONCOVIRUSES**. All known human dsDNA oncoviruses trigger cancerous transformation of cells by a similar mechanism.
- Oncoviruses encode proteins that bind to and thereby inactive cellular proteins known as **TUMOR SUPPRESSORS**.
- **TUMOR SUPPRESSORS** proteins regulate cell cycling or monitor and/or repair DNA damage.
- **Two tumor suppressors** known to be targets of human oncovirus proteins are called **Rb** and **p53.**

1. Rb:

- Rb has multiple functions in the nucleus, all of which are critical to normal cell cycling.
- When Rb molecules are rendered inactive by an oncoviral protein, cells undergo uncontrolled reproduction.
- It is known as **hyperproliferative**.

2. p53:

- known as "**Guardian of the genome**"
- p53 initiate either **cell cycle arrest or programmed cell death** in response to DNA damage
- When p53 inactivated by oncoviral protein, it cannot function and genetic damage persists.
- Hyperproliferation and the lack of programmed cell death are beneficial for virus.

Carcinogenicity of Retroviruses:

- **Retroviruses** exert their oncogenic powers in a different manner.

- Some carry oncogenes captured from host cells many generations ago. Thus they transform the host cell by bringing the oncogene into the cell.
- For example, **Rous Sarcoma virus** carries a mutated, oncogenic **src gene** that codes for an overactive tyrosine kinase.
- **Tyrosine kinase** enzyme is localized to the plasma membrane and phosphorylates the amino acid **tyrosine** in several cellular proteins.
- These Src-targeted proteins are essential in maintaining the cell's ability to respond to normal **anti-growth signals** from other cells and extracellular matrix.
- When **phosphorylated**, they become active and **override these signals**, in effect signaling **unregulated growth**.

Carcinogenicity of HTLV-1 and HTLV-2:

- 1. The human retroviruses HTLV-1 and HTLV-2 transform a group of immune system cells called **T cells** by producing a regulatory protein that sometimes activates genes involved in **cell division** as well as stimulating **virus reproduction**.
- 2. Retroviruses causes integration of a viral genome into the host chromosome in a such a way that viral regulatory elements are near a cellular proto-oncogene. This results in high level of expression of the cellular protein that the gene is now an oncogene. For ex. Some chicken retroviruses induce lymphomas when they are integrated next to the ***c-myc*** cellular proto-oncogene, which codes for a protein that is involved in the induction of either DNA or RNA synthesis.