Lecture 19: Viruses - Effects of viruses on host cells, viruses and cancer

Virus infection may be a factor in development of cancers, although it is important to note that virus infection is not thought to play a significant role in development of most human cancers

- Cancers develop when cells are "released" (usually through a mutation of some sort) from the normal controls on their proliferation, and enter a state of continuous cell division

- Death from cancer is usually due to metastasis, or spread of the malignant cells from the tissue in which they arose

- An association between viral infection and cancer was first demonstrated for Rous sarcoma, a malignancy affecting connective tissue of chickens (note that tumors, both malignant and benign, are named by attaching the suffix "-oma" to the type of tissue affected)

- Malignant transformation of normal cells has been linked to abnormal expression of oncogenes

  - Oncogenes have been identified in the chromosomes of a variety of eukaryotic cell types as well as in the genomes of oncogenic viruses

  - It is assumed that the oncogenes in cells are mutant forms of normal genes, sometimes referred to as proto-oncogenes

  - The most common oncogenes encode synthesis of protein kinases

    - Protein kinases catalyze attachment of phosphate groups (obtained from ATP) to other proteins, modifying the function of the target protein

    - Presumably, the altered protein kinases encoded by oncogenes target proteins that influence control of cell division

  - The association between mutagenic agents and cancers is thought to reflect mutation of proto-oncogenes to oncogenes

- Oncogenic viruses may transform the cells that they infect so that cells multiply in an uncontrolled manner

  - A feature of all oncogenic viruses, which may be DNA or RNA viruses, is that their multiplication involves integration of the viral genome into the host cell's DNA

  - Cells in culture that are transformed by oncogenic viruses typically lose the property of contact inhibition, which normally controls the multiplication of such cells

- To say that a virus is "oncogenic" does not mean that infection with the virus inevitably leads to malignancy

- Among DNA viruses of animals, oncogenic viruses are found among the papovaviruses and herpesviruses

  - Among the papovaviruses are the papilloma viruses that cause begign warts in humans; these have been linked to development of cervical cancers

  - Epstein-Barr (EB) virus, which targets lymphocytes, is a herpesvirus that, at some point, infects about 80% of the human population of the United States

    - EB virus causes infectious mononucleosis in young adults

    - EB virus infection has been linked to Burkitt's lymphoma, nasopharyngeal cancers and (possibly) Hodgkin's disease

  - Infection with hepatitis B virus (HBV) has been associated with increased risk for development of liver cancers

- Among RNA viruses of animals, some of the retroviruses have been linked to cancers
Human T cell lymphotrophic viruses (HTLV 1 and HTLV 2) are associated with leukemias and lymphomas.

Feline leukemia virus (FeLV) is a retrovirus.

No doubt the oncogenic potential of retroviruses is tied to reverse transcription of their genomes.

Oncogene activation leading to malignant transformation appears to be a multistep process, which may explain why infection with oncogenic viruses does not always (or even usually) lead to cancer.

Mutations can affect the function of proto-oncogenes or of other gene products that normally regulate the expression of proto-oncogenes.

Transduction of oncogenes by viruses can lead to abnormal production of oncogene products.

Translocation of proto-oncogenes from one chromosomal locus to another can change their regulation; this is known to occur in Burkitt's lymphoma.

Gene amplification of a proto-oncogene can lead to production of abnormal amounts of the protein that it encodes.

Some viruses are capable of producing latent infections, in which the genome of the virus is carried by host cells without production of virions.

- The classic example of a virus causing latent infections is the herpes simplex virus HSV-1.
  - HSV-1 causes "cold sores" when it is actively multiplying.
  - Between "outbreaks", HSV-1 exists in a latent state in nerve cells.
- Another herpesvirus causing latent infections is varicella-zoster virus.
  - Primary infection with this virus typically results in varicella or "Chickenpox".
  - Herpes zoster, or "shingles", is thought to arise from reactivation of latent virus.
- Latent infection is a common feature of viruses belonging to the Herpesvirus family.

Persistent viral infections, although uncommon, may lead to prolonged disease (Tortora et al. table 13.5).

Prions are infectious proteins responsible for progressive neurodegenerative disorders.

- Several neurological diseases are now understood to be caused by prions.
  - Scrapie, a disease of sheep, is the best-studied example.
  - Bovine spongiform encephalopathy (BSE), "mad cow disease" is also prion-associated.
  - In humans, Creutzfeld-Jacob disease (CJD) is associated with prions.
- Prions are proteins with an abnormal tertiary structure.
  - The protein from which prions are derived, PrpC, is a normal product of many cells.
  - The abnormal form is known as PrpSc (for "Scrapie").
- Propagation of prions is thought to involve interaction between molecules of PrpC and PrpSc (which may be acquired from the environment or produced spontaneously); this causes the molecule of PrpSc to assume the abnormal structure (Tortora et al. Figure 13.21).
- There is concern that persons who consume beef from animals with BSE may become "infected" with prions, leading to new variant Creutzfeld-Jacob disease (nvCJD).