RETROVIRUSES, MOLECULAR BASIS AND INVOLVEMENTS IN CANCER; PROTOONCOGENES AND ONCOGENES.

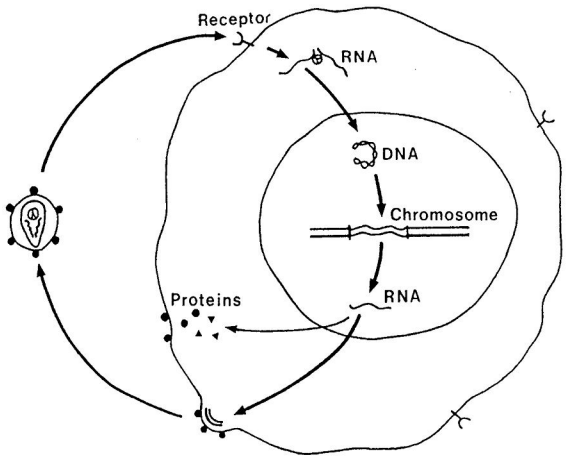
RETROVIRUSES.

Viruses are the smallest infectious agent known and can only replicate inside the cells of another organisms. There are two broad classes of viruses; namely DNA and RNA viruses.
Oncogenic or tumor viruses are viruses capable of inducing the formation of cancer. Tumor viruses are of two distinct types, there are viruses with DNA genomes (e.g. papilloma and adenoviruses) and those with RNA genomes (termed retroviruses).

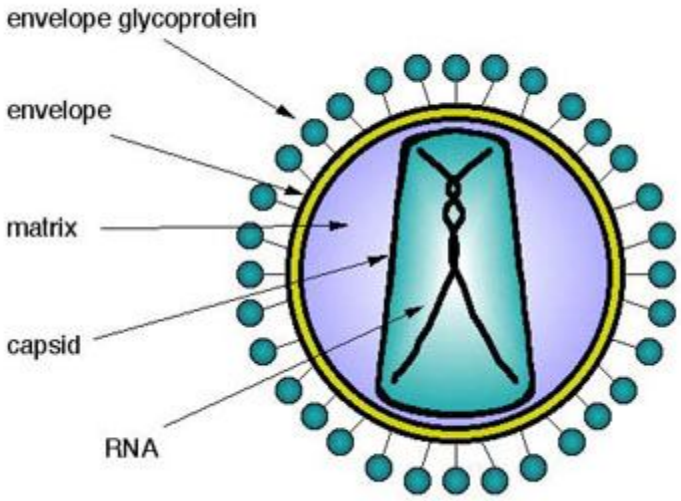
Retroviruses were first associated with malignant diseases in animals more than hundred years ago and have been shown to cause leukemia, lymphoma and other forms of cancer in a wide variety of vertebrate animals ranging from fish to apes. They have been identified in virtually all organisms including invertebrates. The first oncogenic human retrovirus was isolated in1980.

Retroviruses carry diploid, single-stranded RNA genomes in the virion and replicate by forming one double stranded DNA copy in the infected cell, by means of the viral enzyme, reverse transcriptase. This viral genome becomes integrated as a DNA called the 'provirus', into the chromosomal DNA of the host cell and thus persists for the lifetime of the infected cell and its progeny. The proviral genome carries its own promoter and enhancer elements in sequences duplicated at each end of the genome, known as long terminal repeats (LTR).
Expression of the provirus yields full length RNA transcripts that are packaged to become the genomes of progeny virus particles, and mRNA that is translated to provide the viral proteins. (They are transcribed by an RNA dependent DNA polymerase (reverse transcriptase) to produce a double stranded DNA copy of their RNA genome and subsequently serves as a template for gene expression).

Retroviruses are classified into groups including oncovirinae, (Rous Sarcoma Virus ((RSV) - which causes a slow neoplasm in chickens, the first retrovirus to be discovered), Lentivirinae **(**visna virus) and spumavirinae (spumaviruses).



Basic structure of the retrovirus includes an outer envelope which comes from the host cell plasma membrane, coat proteins (surface antigens) ,inside the membrane is an icosahedral capsid containing proteins, that also coat the genomic RNA. There are two molecules of genomic RNA per virus particle with a 5' cap and a 3' poly A sequence. Thus, the virus is diploid. The RNA is plus sense (same sense as mRNA).About 10 copies of reverse transcriptase are present within the mature virus(a polymerase that copies RNA to DNA), Integrase (integrates the viral genome into the host genome), RNase H (cleaves the RNA as the DNA is transcribed so that reverse transcriptase can make the second complementary strand of DNA) and Protease (cleaves the polyproteins).



CANCER

Neoplasm is an abnormal mass of tissue with growth that exceeds and is uncoordinated with that of the surrounding normal tissues and persists in the same excessive manner even after cessation of the stimulus which evoked the change. Cancer is a common term used to refer to malignant neoplasm, they are characterized by diminished control of division, spread or metastasis of dividing cells to other parts of the body and invasion of local tissues. Cancers are the result of a disruption of the normal restraints on cellular proliferation. Three principal groups of agents have been known to cause cancer and these include radiant energy, chemical compounds and biological agents such as viruses. The central feature involved in the occurrence of cancer is damage to cellular DNA which subsequently affects regulatory processes in cells. Approximately 20% of human cancer incidence worldwide is attributable to virus infection.

PROTOONCOGENES AND ONCOGENES

A proto-oncogene is a gene whose protein product has the capacity to induce cellular transformation given it sustains some genetic insult (genes that cause normal cells to become cancerous when they are mutated).
Mutations in proto-oncogenes are typically dominant in nature, and the mutated version of a proto-oncogene is called an oncogene. Often, proto-oncogenes encode proteins that function to stimulate cell division, inhibit cell differentiation, and halt cell death. These activities of proto-oncogene are typically turned off once the developmental processes they regulate are completed. However, if the activity remains high, or if proto-oncogenes are inappropriately reactivated later in life, cancer may occur.

An oncogene is a gene that has sustained some genetic damage and, therefore, produces a protein capable of cellular transformation thus leading to increased cell division, decreased cell differentiation, and inhibition of cell death (taken together, these phenotypes define cancer cells) in other words, an oncogene is a gene that codes for a protein that potentially can transform a normal cell into a malignant cell. It may be transmitted by a virus in which case we refer to it as a viral oncogene.

Oncogenes arise as a result of mutations that increase the expression level or activity of a proto-oncogene. Underlying genetic mechanisms associated with oncogene activation include the following:

- Point mutations, deletions, or insertions that lead to a hyperactive gene product
- Point mutations, deletions, or insertions in the promoter region of a proto-oncogene that lead to increased transcription
- Gene amplification events leading to extra chromosomal copies of a proto-oncogene
- Chromosomal translocation events that relocate a proto-oncogene to a new chromosomal site that leads to higher expression
- Chromosomal translocations that lead to a fusion between a proto-oncogene and a second gene, which produces a fusion protein with oncogenic activity.

There are two classes of these genes in which altered expression can lead to loss of growth control:
(a) Those genes that are stimulatory for growth and which cause cancer when hyperactive. Mutations in these genes will be dominant these are classically referred to as oncogenes. Proto-oncogene's encodes growth factors such as epidermal growth factor (EGF), intracellular proteins to stimulate cell growth and division, Signaling of hormone , GTP-binding proteins involved in signal transduction from a surface receptor to the nucleus etc.

(b) Those genes that inhibit cell growth and which cause cancer when they are turned off. Mutations in these genes will be recessive. These are the anti-oncogenes or tumor-suppressor genes growth suppressors or recessive oncogenes.

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MOLECULAR INVOLVEMENT OF RETROVIRUSES IN CANCER.

Viruses are involved in cancers because they can either carry a copy of one of the proto-oncogene's or can alter expression of the cell's copy of one of these genes.

The following stages occur in the infection process:

1) Binding to a specific cell surface receptor

2) Uptake by endocytosis or by direct fusion to the plasma membrane. The virus may require entry into a low pH endosome before fusion can occur, although some (e.g. HIV) can fuse directly with the plasma membrane

3) RNA (plus sense) is copied by reverse transcriptase to minus sense DNA. Here, the polymerase is acting as an RNA-dependent DNA polymerase. Since reverse transcriptase is a DNA polymerase, it needs a primer. This is a tRNA that is incorporated into the virus particle from the previous host cell.

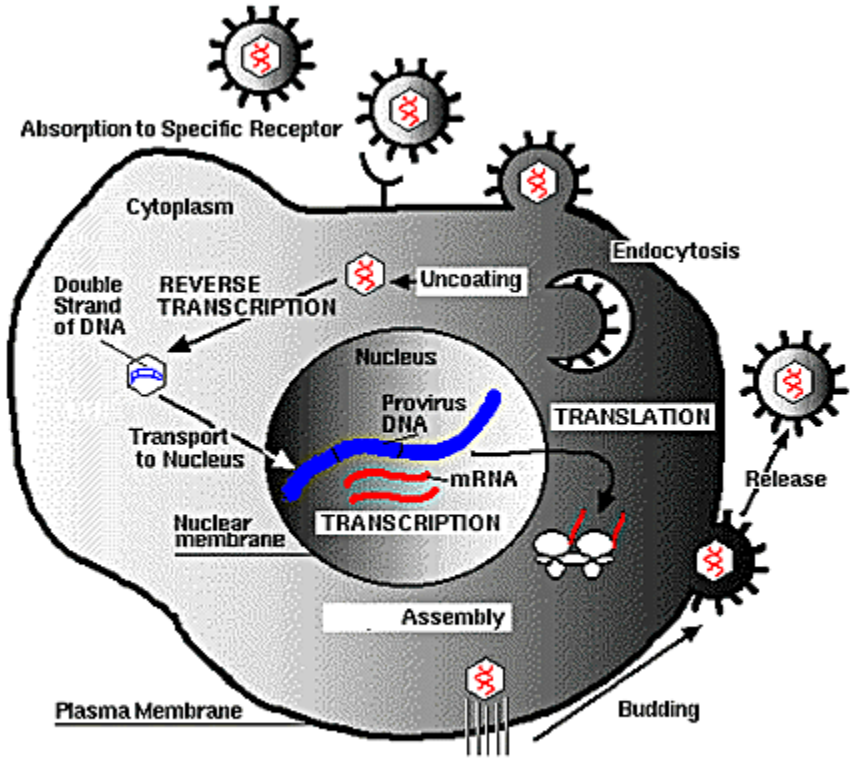
4) RNA is displaced and degraded by a virus-encoded RNase H activity. Reverse transcriptase now acts as a DNA-dependent DNA polymerase and copies the new DNA into a double strand DNA. This DNA form of the virus is known as a provirus.

5) Double strand DNA is *circularized* and *integrated* into host cell DNA (see below) using a virally encoded integrase enzyme. This DNA is copied every time cellular DNA is copied. Thus, at this stage the provirus is just like a normal cellular gene.

6) Full length, genomic RNA (plus sense) is copied from the integrated DNA by host RNA polymerase II which normally copies a gene to mRNA. The genomic RNA is capped and poly adenylated, just as an mRNA would be.

At some frequency, the viral DNA (provirus) integration process into the host genome leads to rearrangement of the viral genome and the consequent incorporation of a portion of the host genome into the viral genome. This process is termed transduction. Occasionally this transduction process leads to the virus acquiring a gene from the host that is normally involved in cellular growth control. Because of the alteration of the host gene during the transduction process as well as the gene being transcribed at a higher rate due to its association with the retroviral LTRs the transduced gene confers a growth advantage to the infected cell. The end result of this process is unrestricted cellular proliferation leading to tumorigenesis. The transduced genes are termed oncogenes. The normal cellular gene in its unmodified, non-transduced form is termed a proto-oncogene since it has the capacity to transform cells if altered in some way or expressed in

an uncontrolled manner. Numerous oncogenes have been discovered in the genomes of transforming retroviruses.
The second mechanism by which retroviruses can transform cells relates to the powerful transcription promoting effect of the LTRs. When a retrovirus genome integrates into a host genome it does so randomly. At some frequency this integration process leads to the placement of the LTRs close to a gene that encodes a growth regulating protein. If the protein is expressed at an abnormally elevated level it can result in cellular transformation. This is termed retroviral integration induced transformation. It has recently been shown that HIV induces certain forms of cancers in infected individuals by this integration induced transformation process.



Retrovirus replication