

Definitions:

- **Oncogene**: a gene of cellular or viral origin that is responsible for rapid and uncontrolled growth in animal cells (c-onc indicates a cellular oncogene)
- **Proto oncogene**: A cellular gene that can undergo modification to a cancer causing gene (the conversion of a normal gene product to a mutated gene and it's resulting protein alteration)
- **Transformation**: conversion of a normal cell line to a cancerous growing cell

Cancer cells are characterized by 3 properties

- 1- lack or loss of control of cell growth
- 2- invasion of local tissue
- 3- spread or metastasis to distal tissues

Chemical Carcinogenesis

Carcinogen - any substance or agent that significantly increases tumor incidence. - any dose, any route

1-4 % of cancers in the US are in due to industrial produced chemicals, there are many more naturally occurring compounds.

Initiating events occurs when a carcinogen interacts with DNA causing a strand break or forming an altered nucleotide called an adduct. DNA replication without repair leads to mutation.

Promoters stimulate initiated cells to form benign tumors (hyperplastic lesions)



Chemical Carcinogenesis

Ames test - determine mutagenicity of compounds. Test uses a Salmonella strain that is readily mutable to histidine independent growth. Only tests for active forms of carcinogens.

Many compounds are inactive until metabolized - often in the ER by the cytochrome P450 enzymes. P450 is a superfamily of genes (>100) normally responsible for degrading xenobiotics. P450 has many variations between species and individuals.

Many of the tobacco carcinogens are activated by various P450 system enzymes. Thus differences in smoking and lung cancer.

Many of the active carcinogens are electrophilic intermediates that react with DNA bases. The modified bases are then mis-read by polymerases leading to oncogene activation or loss of tumor promoter expression.

Most carcinogens fall into 3 categories

Alkylating agents - agents that add methyl or ethyl groups to nucleotides particularly at the N or O atoms not in the ring of the base.

Arylating agents - cause the transfer of aromatic compounds to nucleotides to form an adduct.

Polycyclic aromatic hydrocarbons (PAH) are at the root of several industrial carcinogens. This includes benzo[a]pyrene, found in tobacco and in charcoal grilled meats

Type of agent	General structure	Common examples
A. Alkylating agents	$R-X$	<chem>CCN(C)C=O</chem> N-methylmethanamine <chem>CCN(C)C=O</chem> N-methyl-N-nitrosourea <chem>CCN(C)C=O</chem> N-methyl-N-nitrosourea
B. Arylating	$Ar-C-X$	<chem>C1=CC=C(C=C1)C2=CC=CC=C2</chem> 7,12-dimethylbenz[a]anthracene <chem>C1=CC=C(C=C1)C2=CC=CC=C2</chem> anthracene <chem>C1=CC=C(C=C1)C2=CC=CC=C2</chem> N-acetyl-N'-acetylaminofluorene <chem>C1=CC=C(C=C1)C2=CC=CC=C2</chem> 2-amino-3,4-dimethylbenz[a]anthracene
C. Arylhydroxylamines	$Ar-N-O-X$	<chem>C1=CC=C(C=C1)C2=CC=CC=C2</chem> 2-amino-3,4-dimethylbenz[a]anthracene <chem>C1=CC=C(C=C1)C2=CC=CC=C2</chem> 2-amino-3,4-dimethylbenz[a]anthracene

Most carcinogens fall into 3 categories

Arylhydroxylamines - chemicals that transfer aromatic amines to nucleotides.

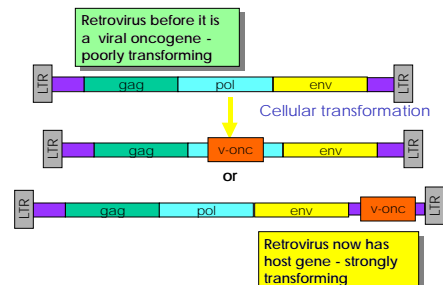
Many of the dyes used these compounds. Aniline dyes caused high rate of bladder cancer. These also require metabolism by P450 before an active nitrogen containing cation reacts with DNA.

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Viral sources of Cancer

Viruses were first found in chickens in 1908 by Ellerman and Bang (erythroid leukemia) and in 1911 (soft cell carcinoma) by Peyton Rous.

Initial "war on cancer" was thought to be primarily viral



Viral sources of Cancer

The mechanism involves viral DNA being integrated into the host cell DNA, and that the protein products of viral genes maintain transformation to the neoplastic state

Most viruses are non-transforming - however, they may play a role in reducing the host cell's ability to inhibit apoptosis.

Cells that are resistant to apoptosis by virtue of the viral genes that they express are more likely to survive genomic damage that will predispose to later neoplastic damage.

KSHV (Kaposi sarcoma-related herpes virus has been implicated in AIDS-associated KS, the most common malignant tumor seen in patients with the acquired immunodeficiency syndrome

Viral sources of Cancer

Viral oncogenes (v-onc, i.e. v-Ras) were used to find a large number of transforming cellular oncogenes.

Viral participation in carcinogenesis has turned out to be rare however there are a few well known cases.

- KSHV (Kaposi sarcoma-related herpes virus has been implicated in AIDS-associated KS, the most common malignant tumor seen in patients with the acquired immunodeficiency syndrome.
- Human papilloma viruses are implicated in cervical cancer. There are over 65 variants of the virus and only 10 or so are high risk strains. 85% of the cervical tumors contain the high risk virus. The viral protein seems to interact with pRb or p53.
- Hepatitis B can lead to liver cancer and causes 0.5 million fatalities per year

Protein (molecular) basis of cancer is found at the genetic level

- Malignant transformation occurs by chromosomal damage, proto oncogene mutation or increase in DNA activity
- DNA is the critical macromolecule in cancer. Daughter cells will retain the mutations and the transformation phenotypes and continue to recruit normal cells into transformation

Genetic Basis of Cancer

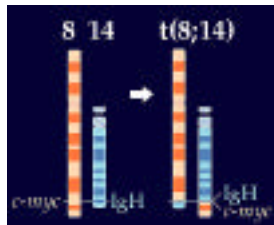
- 1) Translocation of chromosomes - movement of one segment of a chromosome to another
- 2) Viral oncogenes - insert mutated DNA into cell and create oncogenes
 - not normally a cause of cancer but used to find cellular proto oncogenes and study their effects
- 3) Point Mutations - Alterations in specific sequences of critical genes (proto oncogene activation)
 - usually needs several mutations with one or more critical requirements for cancer to develop
- 4) Alteration in promoter/enhancers - can occur due to chromosomal translocation
- 5) Gene amplification

Chromosomal Translocation:

translocation between chromosomes 8 and 14 found in Burkitt's lymphoma (lymph system cancer / leukemia)

- Burkitt's lymphoma is a B cell neoplasm characterized by small noncleaved cells that are uniform in appearance. This neoplasm is one of the fastest growing malignancies in humans. The cells of Burkitt's

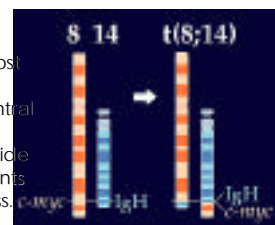
lymphoma are characterized by a specific cytogenetic defect, a balanced, reciprocal translocation of genetic material from the long arm of chromosome 8 to the long arm of chromosome 14.



Chromosomal Translocation:

lymphoma are characterized by a specific cytogenetic defect, a balanced, reciprocal translocation of genetic material from the long arm of chromosome 8 to the long arm of chromosome 14. Two variants of Burkitt's lymphoma are recognized: African and non- African; although very similar in histologic and cytologic features, they have very different

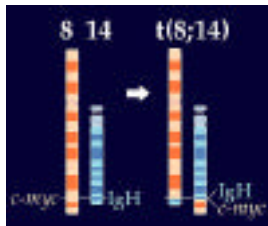
epidemiologic patterns and clinical presentations. African Burkitt's lymphoma presents most often as a jaw or orbital tumor and occurs endemically in central Africa. In contrast non- African Burkitt's lymphoma occurs outside this endemic region and presents primarily as an abdominal mass.



Chromosomal Translocation:

- myc oncogene - proto oncogene found in nearly all tissues normally inactive when cells are not growing contains a binding region for DNA - turns on protein production interacts with tumor suppresser gene (Retinoblastoma protein) c-myc translocated to antibody gene control (high expression levels)

-translocation between chromosomes of 9 and 22 lead to a shortened chromosome - Philadelphia chromosome (95% of adult chronic mylogenetic leukemia)



Another translocating oncogene

abl oncogene - also found in most tissues proto oncogene abl a non receptor tyrosine kinase with SH2, and SH3 domains. Also interacts with P53 and DNA activation of c-abl not clear but seems to be correlated with general DNA damage and translocation.

Oncogene is now fused with a new protein and abl loses part of its kinase regulation - constitutively active

Transformation of proto oncogene to oncogene (i.e. how to turn the cell on)

Tyrosine kinase was first discovered oncogene - Src

- Normal gene found in chickens and retrovirus contain parts of the Src gene - specifically the SH1 domain (the protein tyrosine kinase)
- Leads to increased phosphorylation of several cellular proteins which are normally on to increase cell growth
- Leads to increases in inositol and calcium signaling
- There is little control. Now the pathway is always "on" leading to increase uncontrolled cell growth

Receptors can be cause of cancers - Erb - avian erythroblastosis virus

- c-erb codes for an epidermal growth factor receptor.
- v-erbB is a truncated receptor- extracellular portion missing
- Alters the structure activity of the internal kinase domain that leads to activation of tyrosine phosphorylation - constitutively activated EGF pathway
- several forms of erb oncogene some cancerous
- mutated c- erb found in brain and breast cancer
- this type of oncogene is common for several different receptors (tyrosine kinase not seven transmembrane receptors)

Intracellular proteins can also be responsible for causing cancer - Ras - first found as several different viral oncogenes in sarcoma viruses in rats (Rat Sarcoma)

Ras- 21 kDa protein first called p21

- member of large family of monomeric GTP binding proteins (similar to the heterotrimeric G protein subunit)
- mutations occur at three amino acids at the phosphate binding site any change in glycine 12 other than proline lead to oncogene conversion
- ras oncogene has lost the ability to hydrolyze GTP
- stays in the GTP activated form - Raf activation
- treated by inhibiting isoprenylation at the CAAX box by farnasyl transferase inhibitor (lovastatin)
- tobacco and UV radiation are known to mutate cellular ras

Mutations in transcription factors are also found

- Over expression of c-myc gene (found in nearly every tissue)
- Increased c-myc protein is due to enhancer and promoter insertion for the normal myc gene. This of course leads to increased myc product.
- Can also happen in translocation (see above) - result is high level of active transcription factor and ultimate increases in other gene expression