The Process of Carcinogenesis

Steps of tumor development

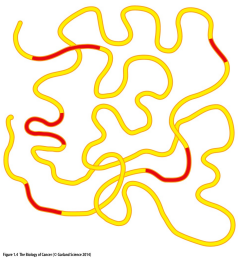
- **Initiation: essential step that is latent until next step. Often occurs as DNA damage in stem cells**
- **Promoting Agent: Typically not a carcinogen but a chemical that can induce cells to grow.**
- **Growth Inhibition: Normal control of cell growth can influence tumor growth .**

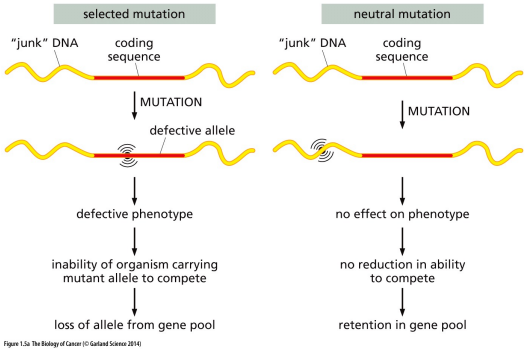
Initiating Agent	Promoting Agent	Growth Inhibitors
•Chemical-Carcinogens •Viruses •Radiation •UV Light •Replication Errors	•Specific Promoters •Inflammation •Hormones •Normal growth promoters	•Hormones - therapeutic or physiological •Normal Growth Inhibitors -age, surgery, radiation

Mutations Drive Cancer

Human Genome – 3 billion bp

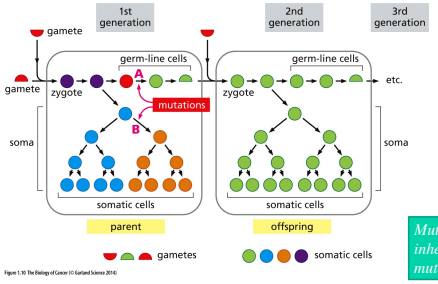
- 1.5% codes for proteins ~ 45 million bp
- Rest is "junk" DNA
- ~550 "cancer genes"
- Ignore upstream regulators
- ~8250,000 bp "cancer coding"
- Only some bp will lead to cancer
- Multiple Genes must be altered 3-12
- Odds of getting a "random" mutation is difficult and cumulative





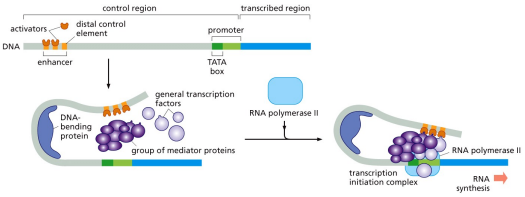
Transmission of Mutations

- Germ cell – sperm and egg: inheritable or new mutation must take place in gonadal tissue
- Somatic cell – All other cells are soma. Genetic alterations (mutations) are passed on to daughter cells but not to offspring



Mutation A is inheritable, not mutation B

Basic Molecular Biology



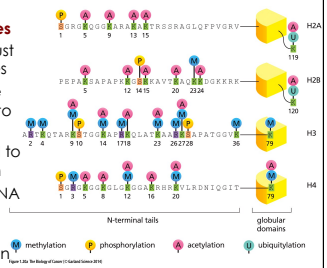
Gene expression depends on multiple proteins and DNA regions.

- Coordinated expression of multiple genes depends on a few common TFs
- Two classes: Housekeeping and tissue specific genes
  - Differentiation relies on ~ 1000 tissue specific genes being appropriately activated
  - ~ 5000 routine genes – metabolism and other cellular needs
  - Many unexpressed genes

Chromosome "Activation"

More than just bound to histones

- TF and RNA polymerase must bind "unwind" from histones
- Multiple modifications drive histone – DNA interactions to modulate TF binding
- Phosphorylation – can lead to condensation of chromatin
- Acetylation limits histone-DNA binding creating "active" chromosome hot spots
- Methylation supports protein binding and limits gene expression



Epigenetic inheritance

Heritable genetic traits not caused by DNA mutations – long term stable gene regulation

- Histone modification controls large sets of gene expression
- Methylation regulates TF near promoter regions
- All ensure the daughter cells maintain the same set of "active genes

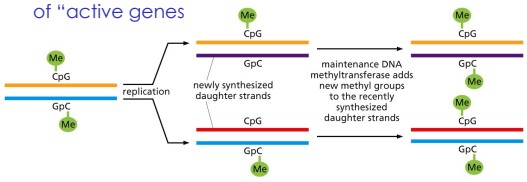


Figure 1.21 The Biology of Cancer (© Garland Science 2014)

Causes of cancer

•80% of human cancers are estimated to be caused by environmental factors - such as diet, lifestyle and occupation

•biggest two causes are tobacco and diet (60 % of total cancer moralities)

•heredity is a major factor in some cancers (breast and colon)

Causes of cancer

Cancer are cells out of control - signal transduction without the regulation

•loss of normally controlled cell growth

•final result usually from loss of both an on and an off signal

•Signals controlling growth clock - cell cycle - are mutated

Stimulatory pathways - this pathway will become hyperactive if a mutation causes any component, such as growth factor receptors to issue stimulatory messages autonomously, without waiting for commands from upstream.

- growth factor receptors mutated so the intracellular kinase domain is "on"
- cytosolic signaling molecules improperly activated
- nuclear DNA binding proteins turned on
- Growth factors or hormones over-produced without control

Inhibitory pathways - conversely inhibitory pathways will shut down when some constituent, such as a cytosolic protein is eliminated and thus breaks down the off signaling path

- specific tumor suppresser genes exist
- some are involved in normal cell cycle regulation
- some are inhibitory for specific stimulatory proteins (EGFR and Ras)

Tumors arise from normal tissues

Tumor cells which have invaded and proliferate forming new colonies (tumors) are metastases

- Primary tumor is created from founding tissue
- Tumors which have not breached basal membrane or invaded other tissues are benign
- Tissues that spread are malignant
- Adult Stem Cells – can collect mutations and form tumors

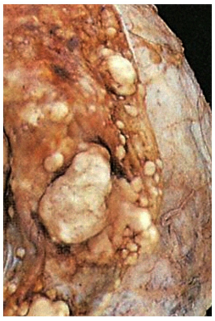
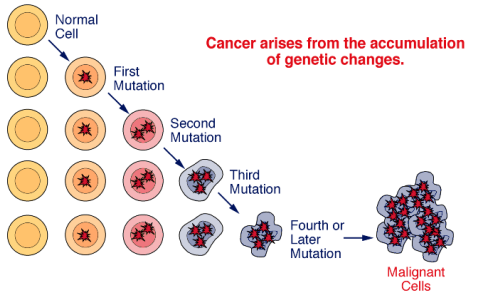


Figure 2.2c The Biology of Cancer (© Garland Science 2014)

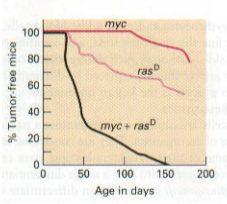
Understanding the Molecular Basis of Cancer



The Process of Carcinogenesis

Carcinogenesis is a multistage event

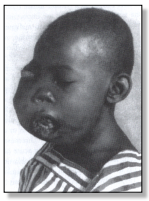
- **Application of a single cancer-producing agent (carcinogen) does not lead to tumor development**
- **Most cancers are collaborative events**



Forces That Influence Cancer

There is no single cause of cancer.

Genetics – Breast and ovarian cancer (BRCA gene), Li-Fraumeni Syndrome, colorectal cancers



Enviroment – smoking contributes to nearly 1/3 of all cancer deaths. Smoking increases risk 1,200 fold for women and 2,000 fold for men.

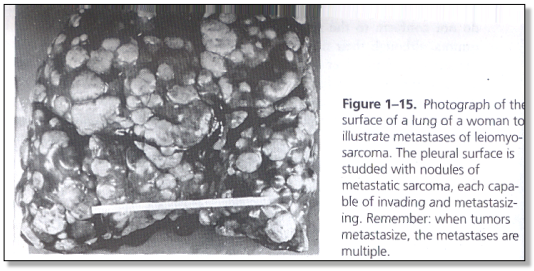


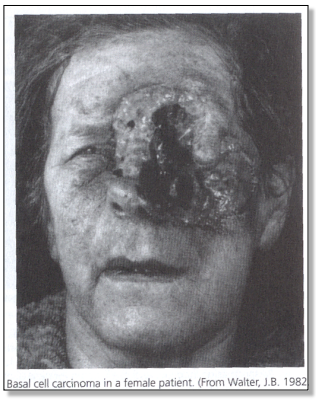
Figure 1–15. Photograph of the surface of a lung of a woman to illustrate metastases of leiomyosarcoma. The pleural surface is studded with nodules of metastatic sarcoma, each capable of invading and metastasizing. Remember: when tumors metastasize, the metastases are multiple.

Forces That Influence Cancer

Diet – Contribution can vary. High fiber, fruit and vitamins can decrease risk and high fat increases

Virus – Limited to a few types of cancer – stomach, cervical and Kaposi's sarcoma (AIDS-related)

Factor	%
Tobacco	33
Diet	30
Infection	9
Hormones	7
Radiation	6
Occupation	3
Alcohol	3
UV light	1



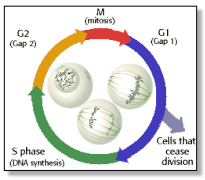
Basal cell carcinoma in a female patient. (From Walter, J.B. 1982)

Progression of Cancer Control of the Cell Cycle

Oncogene: "gene capable of causing cancer"

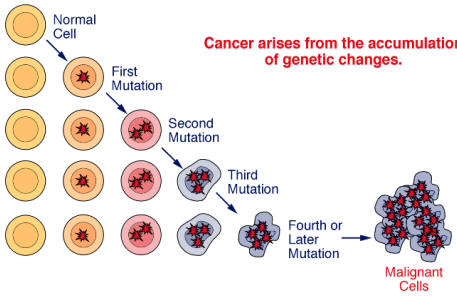
Tumor Suppressor: "anti-oncogene"

On Switch

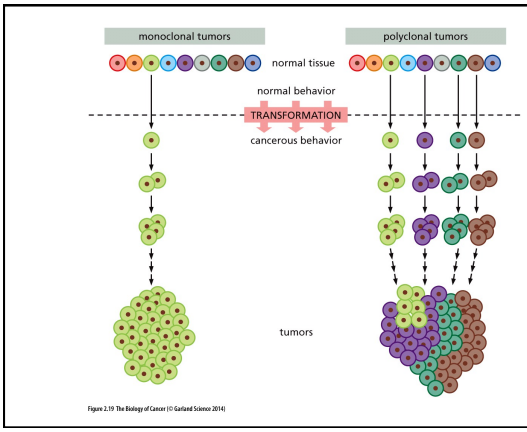


Off Switch

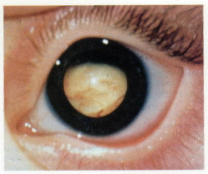
Understanding the Molecular Basis of Cancer



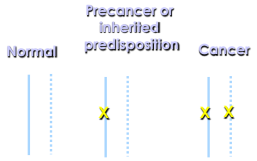
Cancer arises from the accumulation of genetic changes.



Multiple Hit Theory of Tumor Suppressor Cancer

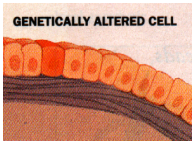


•5/100,000 children get retinoblastoma
•40% of cases are familial remainder result from both genes being mutated

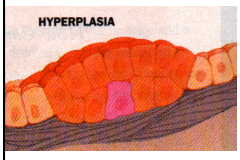


Model for the two hit recessive control of cancer

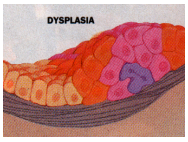
Tumor development occurs in stages



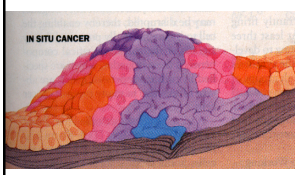
1) **Genetically altered cell -** tumor development begins when a single cell within a normal population sustains a genetic mutation that increases when it would normally rest



2) **Hyperplasia**
The altered cell continues to grow and the daughter cells continue to look normal but they produce too much - after years some of these cells suffer another mutation that further loosens controls on cell growth

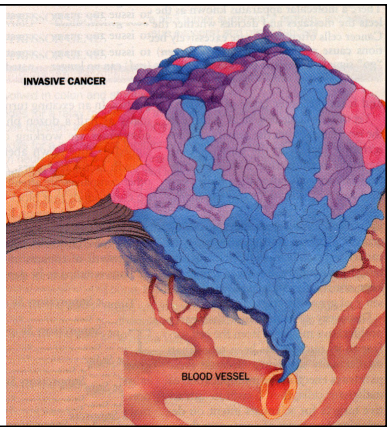


3) **Dysplasia**
In addition to proliferation excessively, the mutated cells begin to appear abnormal in shape and orientation - morphology changes; After time an additional mutation occurs



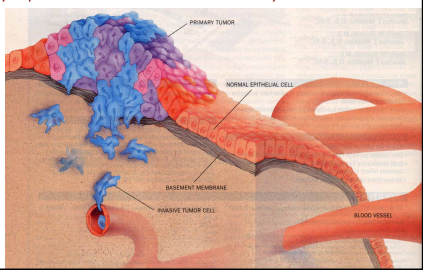
4) **In situ cancer**
The effected cells become still more abnormal in growth and may or may nor have begun to lose containment in the original tissue. Additional cells gain another mutation

5) **Invasive cancer** if the genetic changes allow the tumor to begin invading underlying tissue and to shed cells into the blood stream or lymph, the mass is considered to have become malignant. The renegade cells are likely to establish themselves throughout the body; these may become lethal by disrupting a vital organ



Invasion and Metastasis - the method which spreads cancer through out the body. First cancer cells detach from the primary tumor and breach the basal membrane surrounding a blood vessel and are free to circulate via the blood stream. Eventually a cancer cell may lodge in a capillary or lymph and create a secondary tumor.

- Less than one in 10,000 cancer cells that escape the primary tumor survives to colonize another tissue



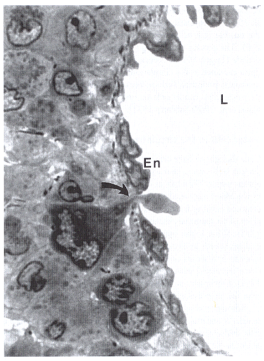
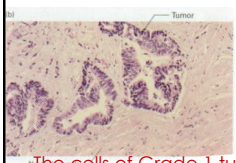


Figure 2–9. Cancer cells gain access to blood circulation by diapedesis. The cancer cell traverses a small opening (arrow) between endothelial cells (En) of the vessel to gain access to the lumen (L). (From Sona, M.J., Reilly, A.A., Parsons, D.F., and Hussain, M. 1986

Tumors Grades

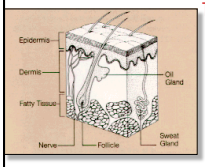
A malignant tumor can be removed and classified for tumor grade and the degree of cell differentiation.



The term "differentiated" describes the extent to which cancer cells are similar in appearance and function to healthy cells of the same tissue type. The degree of differentiation often relates to the clinical behavior of the particular tumor.

The cells of Grade 1 tumors are often well-differentiated or low-grade tumors, and are generally considered the least aggressive in behavior. Conversely, the cells of Grade 3 or Grade 4 tumors are usually poorly differentiated or undifferentiated high-grade tumors, and are generally the most aggressive in behavior.

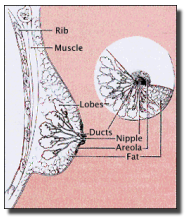
Melanoma



The most serious cancer of the skin. In Western countries, the number of people who develop melanoma is increasing faster than any other cancer. In the United States, for example, the number of new cases of melanoma has more than doubled in the past 20 years.

Melanoma occurs when melanocytes (pigment cells) become malignant.

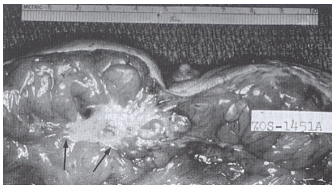
- Melanoma can occur on any skin surface. In men, it is often found on the trunk or the head and neck. In women, melanoma often develops on the lower legs. Melanoma is rare in black people and others with dark skin.
- Melanoma is one of the most common cancers in young adults.

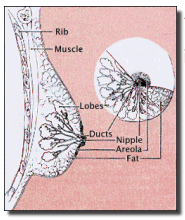


Breast Cancer

Other than skin cancer, breast cancer is the most common type of cancer among women in the United States. More than 180,000 women are diagnosed with breast cancer each year.

- The exact causes of breast cancer are not known. However, studies show that the risk of breast cancer increases as a woman gets older. This disease is very uncommon in women under the age of 35. Most breast cancers occur in women over the age of 50, and the risk is especially high for women over age 60. Also, breast cancer occurs more often in white women than African American or Asian women.



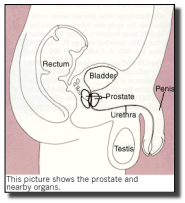


A report from the National Cancer Institute (NCI) estimates that about 1 in 8 women in the United States (approximately 12.8 %) will develop breast cancer during her lifetime.

from age 30 to age 40	1 out of 257
from age 40 to age 50	1 out of 67
from age 50 to age 60	1 out of 36
from age 60 to age 70	1 out of 28
from age 70 to age 80	1 out of 24
Ever	1 out of 8

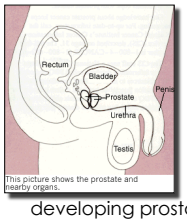
- 1 in 8 means that, if current rates stay constant, a female born today has a 1 in 8 chance of developing breast cancer sometime during her life.
- Considering time and race - age 50, a cancer-free black woman has about a 2.5-percent chance of developing breast cancer by age 60, and a cancer-free white woman has about a 2.8-percent chance

Prostate Cancer



- Prostate cancer is the most common type of cancer in men in the United States (other than skin cancer). Of all the men who are diagnosed with cancer each year, more than one-fourth have prostate cancer.

The causes of prostate cancer are not well understood. Doctors cannot explain why one man gets prostate cancer and another does not.



Risk Factors

Age. In the United States, prostate cancer is found mainly in men over age 55. The average age of patients at the time of diagnosis is 70.

Family history. A man's risk for developing prostate cancer is higher if his father or brother has had the disease.

- **Race**. This disease is much more common in African American men than in white men. It is less common in Asian and American Indian men.
- **Diet and dietary factors**. Some evidence suggests that a diet high in animal fat may increase the risk of prostate cancer and a diet high in fruits and vegetables may decrease the risk.

Organization of Tumor cells

Epithelial tissues give rise to most cancer types

- Sheets of cells that line inner or outer walls of organs and surfaces of the body
- These cells come from endodermal / ectodermal germ layers
- ***Cancers from epithelial tissues are called "carcinomas"***

Epithelial Carcinomas

Protective layer cells which form tumors are squamous cell carcinoma – skin (keratinocytes) are an example

Epithelial cells which secrete substances form adenocarcinoma cancers

Tissue sites of more common types of adenocarcinoma	Tissue sites of more common types of squamous cell carcinoma	Other types of carcinoma
lung	skin	small-cell lung carcinoma
colon	nasal cavity	large-cell lung carcinoma
breast	oropharynx	hepatocellular carcinoma
pancreas	larynx	renal cell carcinoma
stomach	lung	transitional-cell carcinoma
esophagus	esophagus	(of urinary bladder)
prostate	cervix	
endometrium		
ovary		

Table 2.1 The Biology of Cancer (© Garland Science 2014)

More definitions

Stromal cells – connective tissues of any organ and supports tissue surrounding other tissues and organs – produce connective proteins, extracellular matrix and secrete factors

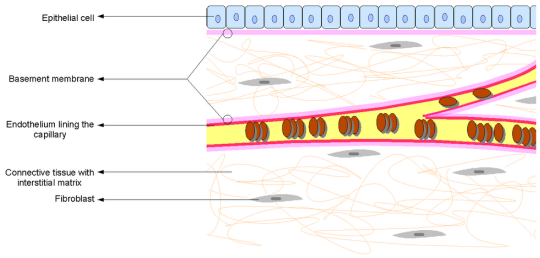
- In cancer, changes in the stroma drive invasion and metastasis – malignancy. Together with the tumor cells, stromal cells are a critical part of the tumor cell microenvironment.
- These cells are not cancerous but support cancer growth and determine location of metastatic disease. Bone, breast, other tissue stromal cells secrete different proteins and factors supporting specific tumor metastasis
- Potential target for chemotherapy

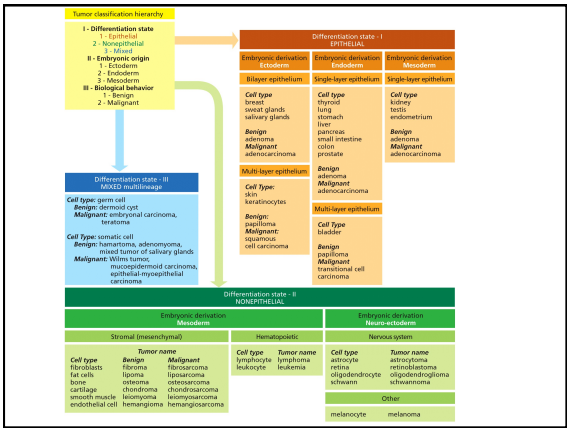
Basement membrane – non cellular region of tissues that separates epithelium from underlying connective tissue – matrix (mixture of proteins – not cells)

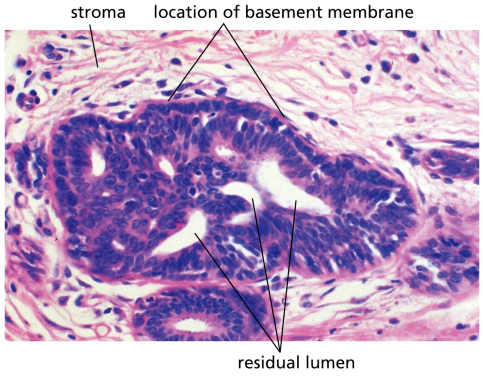
Lumen cells – Those epithelial cells which face the hollow core (inside space) of a cavity

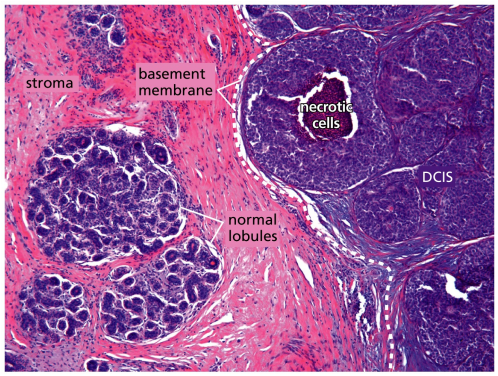
Fibroblast cell – Synthesize extracellular matrix and collagen providing structural framework for stromal cells to grow – have potential to mature into different cells "blast" chondroblast, collagenoblast or osteoblast

Illustration depicting extracellular matrix in relation to epithelium, endothelium and connective tissue









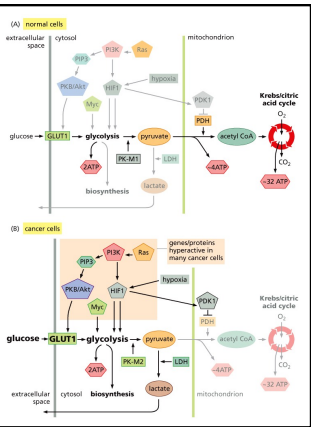
Warburg Effect

Hypoxia – anaerobic metabolism in tumor cells before angiogenesis

- Low ATP production but faster than Krebs cycle
- Formation of glycolytic intermediates for biosynthesis
- Takes place in tumor cells even when oxygenated

Pyruvate Kinase – M1 isoform usually expressed in most tissues (not liver) M2 form mostly in embryonic tissue

- M2 is expressed in carcinomas – M2 has slower Kcat – turnover rate: "backs up" glycolysis forcing lactate production
- Resulting in acid production



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 begnin tumors (hyperplastic lesions)

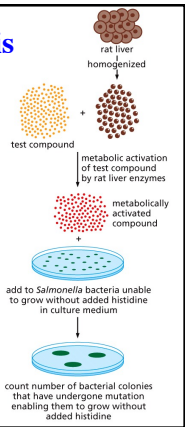
Chemical Carcinogenesis

Ames test - determine mutagenicity of Test uses a Salmonella strain that is readily mutable to histadine 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 electrohilic 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.

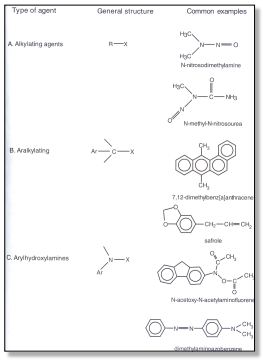


Most carcinogens fall into 3 categories

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.

Aralkylating 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 benso[a]pyrene, found in tobacco and in charcoal grilled meats



Most carcinogens fall into 3 categories

Arylhydroxylamines - chemicals that transfer aromatic amines to nucleotides.

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