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NEOPLASIA

- Literally Means New growth
- An altered cell population
- Nonuseful growth
- Unresponsive to normal growth control
- *"A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissue, and persists in the same excessive manner after the cessation of the stimulus which evoked the change"*

R. A. Willis (1972)

FEATURES OF NEOPLASIA

- An irreversible process
- The cell has undergone a fundamental and permanent modification (DNA damage)
- End result is uncontrolled (autonomous) cell growth

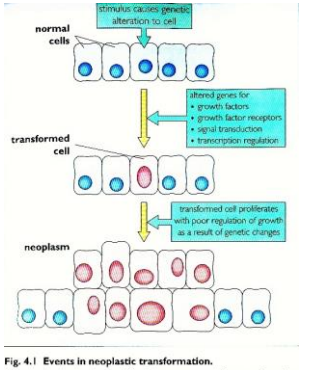

Fig. 4.1 Events in neoplastic transformation.
Normal cells develop abnormalities in key genes regulating growth and are transformed into neoplastic cells.

NOMENCLATURE AND CLASSIFICATION

- For a pathologist and clinician, Nature and significance of the lesion.
- Neoplasms are classified on various basis:
  - Naked eye appearance
  - Histogenic
  - Histological
  - Behavioural
  - Aetiological
  - Functional

NAKED EYE APPEARANCE

- **Clinical examination of the patient and the organ of origin.**
- **Naked eye examination reveals growth of special character as cauliflower like or scirrhous (hard).**

HISTOGENIC

- Based on cell type of origin
- Body cells can be divided into
  - Epithelial
  - Connective tissue
- In neoplasia – difficult to distinguish between epithelial and mesenchymal cell origin.
- For example neuronal epithelial cell neoplasm may resemble squamous or glandular epithelium.

- A few neoplasms contain both cell type, i.e., epithelial and connective tissue.
- Teratoma is an example of germ cell neoplasm, occurs most frequently in the **ovary** or **testis** – may contain cells from all three germ layers which may include bone, skin, nervous tissue, muscle, hair and others.

HISTOLOGICAL

- In complete **anaplasia**, actual appearance of the neoplastic cells may be used as basis for classification.
- Glandular cells without gland formation can be described as polygonal cells, spheroidal cells or anaplastic.
- A term "**squamous cell carcinoma**" is used to describe a tumour with a squamous differentiation of cells rather than to indicate its origin from stratified squamous cells.

BEHAVIOURAL CLASSIFICATION

- Neoplasm based on behaviour has been classified into **benign** (non-invasive) and **malignant** (invasive).
- Intermediate type of behaviour do exists.
- The capsule formation – characteristic of benign neoplasm.
- Benign neoplasms grow slowly and usually show few mitotic cells.
- Malignant neoplasms always invade the surrounding tissues and spread (metastasis) to even distant part/tissue through lymphatics and blood vessels.
- Malignant neoplasms show much higher mitotic cells

AETIOLOGICAL CLASSIFICATION

- Since the cause of most of the neoplasms is unknown so this classification now is impractical.

FUNCTIONAL CLASSIFICATION

- This classification is based on the clinical and pathological changes produced by the Product, e.g., glucagonoma, insulinoma etc.
- This classification is also not regarded as satisfactory.

CURRENTLY USED CLASSIFICATION

- **Tissue of origin** and the **behavioural pattern** forms the basis of the current classification and is followed by a **histologic** description.

TUMOR NOMENCLATURE AND CLASSIFICATION

- **Mesenchymal / Connective Tissue**
  - **Suffix - oma for benign**
  - **Suffix - sarcoma for malignant**

- **Fibroma**
  - **Benign tumors of fibroblasts**
- **Fibrosarcoma**
  - **malignant tumor of fibroblasts**

Chondroma --- Chondrosarcoma

EPITHELIAL TUMOURS

- **Suffix - oma for benign**
- **Suffix - carcinoma for malignant**

- **Papilloma**
- **Benign tumors of surface epithelium**
- **Carcinoma**
  - **malignant tumor of epithelial origin**
- **Adenoma**
  - **Benign tumors of glandular epithelium**
- **Adenocarcinoma**
  - **Malignant glandular tumor**

- **Classification of neoplasms**
  confusion persists
  melanoma
  does not indicate malignancy

MORPHOLOGY AND BEHAVIOUR OF NEOPLASMS

- **Benign** and **malignant** neoplasms
- Neoplasms do not always fall into one of the categories.
- histologic features of malignancy but behave in a benign fashion.
- Gross appearance -- highly variable,

- **General rule -- whether benign or malignant:**
  - **Differentiation**
  - **Growth**
  - **Local invasion**
  - **Metastasis**

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- General rule -- whether benign or malignant include
  - Differentiation
  - Growth
  - Local invasion
  - Metastasis

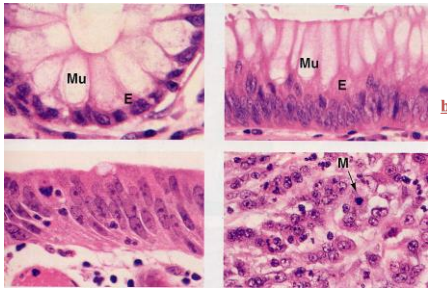
DIFFERENTIATION

Extent to which cells resemble normal cells :

- morphologically
- functionally
  - Well differentiated
  - Moderately differentiated
  - Poorly differentiated
  - Anaplastic

- Benign tumours usually closely resemble normal cells (well differentiated).
- Malignant tumours show a range of abnormal differentiation – well to undifferentiated (anaplastic)

DEGREE OF TUMOR DIFFERENTIATION: COLON



normal — benign

Well-differentiated malignant neoplasm
Nuclei irregular in shape and arrange-ment, no mucin, nuclei stratified, nucleoli large and irregular in shape

Poorly differentiated neoplasm
No resemblance to colon epithelia
Mitotic figures present, haphazard arrangement

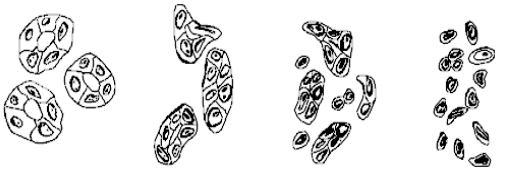
- **Tumour grade: assigned by the pathologist to reflect the degree of differentiation.**

NEOPLASIA…Grading

- Grade 1 --- >75% cells differentiated
- Grade 2 --- >50% cells differentiated
- Grade 3 --- >25% cells differentiated
- Grade 4 --- <25% cells differentiated

BIOLOGY OF TUMOR

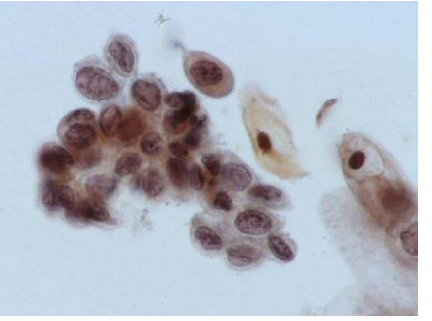
- **Grading – Differentiation**
- **Staging – Progression (in growth)**



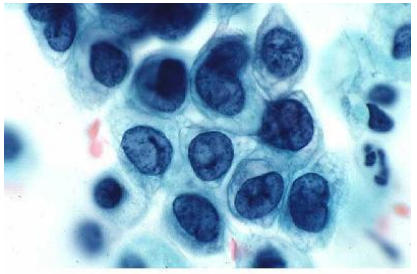
Cytology – individual cell morphology

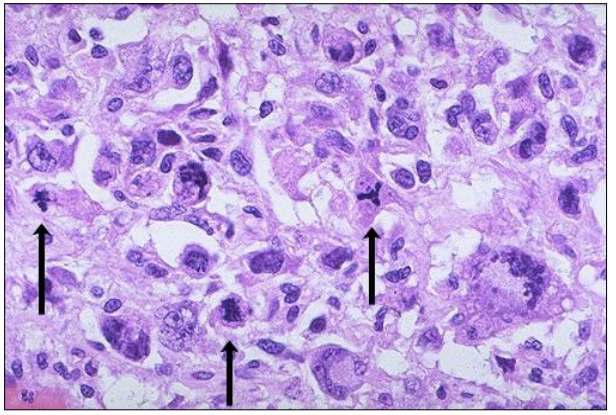
- **Pleomorphic**
  - **Shape**
  - **Size**
- **Nuclear/cytoplasmic ratio (N/C) → 1:1 (N 1:4 – 1:6)**
- **Mitoses**

- Pleomorphism: variation in size and shape

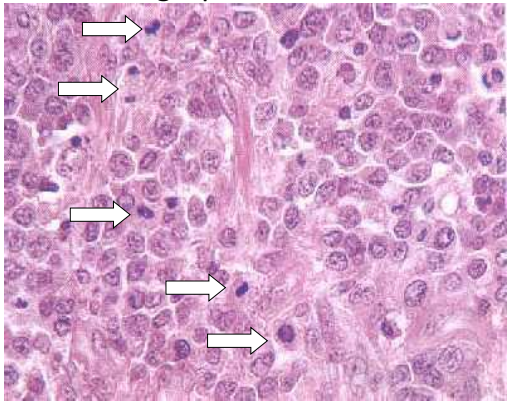


- Abnormal nuclear morphology: hyperchormatic (abundant DNA), increased N:C ratio (normal 1:4 - 1:6)





Histologic picture of Mitosis:



GROWTH

- **Malignant neoplasms grow faster which is probably not very true.**
- **It is observed that length of the mitotic cycle is shorter in normal jejunal epithelial cells than a faster growing neoplasm.**
- **The normal cell cycle time in bone marrow is 18 hours, while in acute myeloblastic leukaemia it is 80 hours and in chronic myeloblastic leukaemia is 120 hours.**

- The rate of loss of cells by necrosis and by exfoliation is the most important factor in determining the overall growth rate.
- The growth rate is also influenced by hormones and the outside pressure,
  - e.g., benign smooth muscle neoplasm (leiomyoma) of the uterus in women may grow rapidly during pregnancy and may cease growing or undergo atrophy after the menopause.

Average Growth Fractions and Doubling Times of Human Cancers

Human cancer	Growth fraction (%)	Doubling time (days)
Embryonal tumours	90	27
Lymphomas	90	29
Sarcomas	11	41
Squamous cell carcinomas	25	58
Adenocarcinomas	6	83

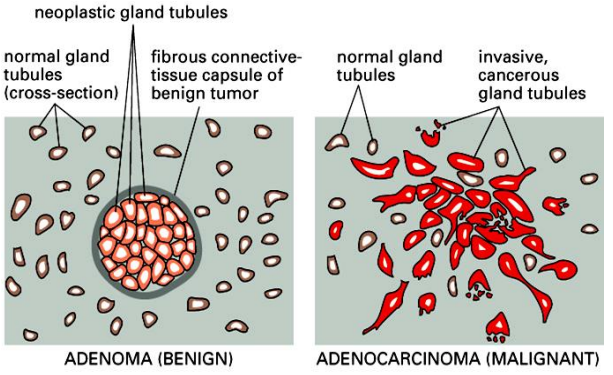
Tumour stage: assigned by the clinician

- Stage I mean the tumour is smaller than 1 cm diameter, without metastases
- Stage II mean the tumour is larger than 1 cm and/or is symptomatic and/or there are metastases to the regional lymph nodes
- Stage III mean the tumour has infiltrated a non-resectable structure and/or there are distant metastases

LOCAL INVASION

- Benign neoplasms generally do not invade the surrounding tissue
- Benign neoplasms remain localized and usually have a fibrous capsule cover.
- Malignant neoplasms, however, invade and infiltrate the surrounding tissue.
- Malignant neoplasms do not have well developed capsule.

Benign tumors are contained, malignant tumors are invasive

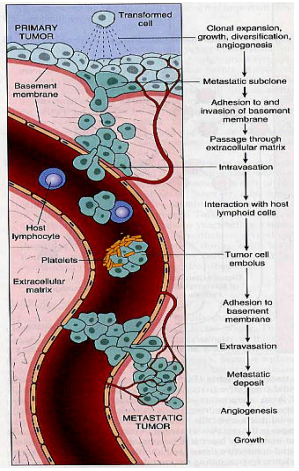


METASTASIS

- Metastasis gene (**cyclin D1 gene**); c-erb-B2 oncogene correlates with metastasis in some breast carcinomas.
- Spread of the neoplasms to distant places, not contiguous with the primary mass
- The neoplasms those metastasize are called malignant.
- However, not all malignant neoplasms metastasize.

- Spread through lymphatics occur to the regional lymph nodes.
- Spread of neoplasms through lymphatic is one of the major mechanism and is a typical route for spread of carcinomas.
- Spread of neoplasms via blood vessels is important and is typical of sarcomas while less so by carcinomas.

- Metastasis also occur by exfoliation (sloughing) and implantation.
  - This spread occurs when a carcinoma reaches to a serosal surface and desquamates.
  - Carcinoma of the colon may penetrate the wall of the gut and re-implant in the peritoneal cavity.



Benign

- Slow growing,
- capsulated,
- Non-invasive
- do not metastasize,
- well differentiated,
- suffix “oma” eg. Fibroma.

Malignant

- Fast growing,
- non capsulated,
- Invasive & infiltrate
- Metastasize.
- poorly differentiated,
- Suffix “Carcinoma” or “Sarcoma”

QUESTIONS ???

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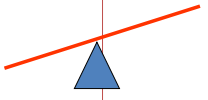
PATHOGENESIS OF NEOPLASIA

- GROWTH PROMOTING
- **PROTO-ONCOGENES**

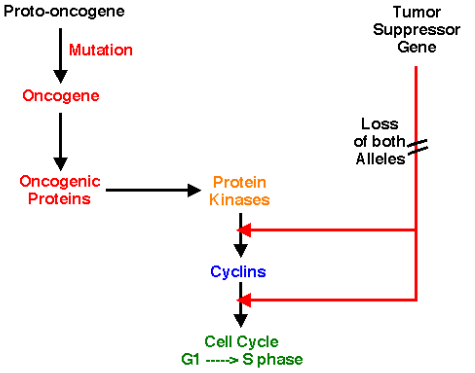
- GROWTH INHIBITING
- CANCER SUPPRESSOR GENES
- **ANTI-ONCOGENES**



-GENES REGULATING CELL DEATH
APOPTOSIS

INDIRECT

REPAIR GENES



Neoplasia, or uncontrolled cellular proliferation, can result either from mutations that "turn on" the oncogenes that stimulate growth, or from mutations that result in loss of tumor suppressor genes and their products that inhibit growth.

ONCOGENES

- **Oncogenes were originally discovered in transforming retroviruses ("the RNA tumor viruses").**
- **"Viral oncogenes" -- cancer-producing genes**
- **More than thirty proto-oncogenes have been studied in detail.**
- **Oncogenes are slightly altered forms of proto-oncogenes ("mitogenes")**

- **THERE ARE SEVERAL FAMILY GROUPS, BASED ON THE PROTEINS THEY PRODUCE:**
  - **Classic tyrosine kinase proto-oncogenes**
  - **GTP-binding protein proto-oncogenes**
  - **DNA-binding protein proto-oncogenes**
  - **Growth factor protein proto-oncogenes**
  - **Protein growth factor receptor proto-oncogenes**
  - **Enhancer binding protein proto-oncogenes**
  - **Transcription initiation factor proto-oncogenes**
  - **Master switch proto-oncogenes**
  - **Left overs -- oncogenes that do not (yet) fit into any family.**

TRANSFORMATION OF PROTO-ONCOGENE

- **Two broad categories of changes**
  - **Changes in structure of genes, now having an aberrant function.**
  - **Changes in regulation of gene expression, now resulting enhanced or inappropriate production of though structurally normal growth promoting protein.**

Conversion of Cellular Proto-oncogenes to Oncogenes

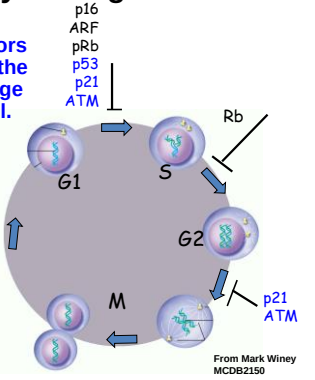
- The known mechanisms of proto-oncogene activation and well-studied examples include:
  - translocation: c-myc, c-abl;
  - promotor insertion: c-myc, c-erb B;
  - point mutation: c-ras;
  - deletional mutation: c-erb B;
  - amplification: c-myc.

TUMOR SUPPRESSOR GENES (ANTI-ONCOGENES)

- **tumor-suppressor genes keep cells benign, even when the oncogenes are activated.**
- **To lose their anti-cancer effect, both copies must be altered – RECESSIVE GENES**

Most Tumor Suppressors are Negative Cell Cycle Regulators

Some Tumor Suppressors Block the Cell Cycle in the Presence of DNA Damage or Incomplete DNA Repl.



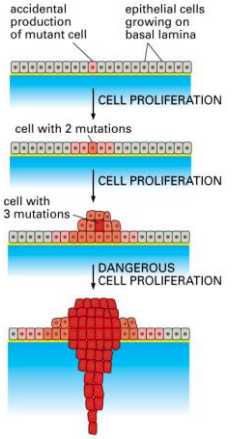
In their absence, cells with damaged DNA keep generating new cells without fixing the damage

From Mark Winey MCDB2150

LATE PROGRESSION

- **Once its growth genes have been mutated and its genome perhaps destabilized,**
  - **cancer is still not a threat until it has developed the ability to invade, to induce its own blood supply, and (usually) to spread to distant sites.**

The progression from a normal single cell to one with unusual properties and then on to a full-blown metastatic cancer cell requires multiple mutations. These accumulate to give the cell increasingly deviant and dangerous properties



APOPTOTIC GENES

- The apoptotic genes are responsible for cell survival.
- both apoptosis promoting and apoptosis inhibiting genes are present.
- The names of apoptotic genes start with a letter "b", e.g.,
  - bcl-2, bcl-x, bax, bag, bad and many more yet to come.
  - The gene bcl-2 is apoptosis inhibitory.
    - This gene is located on chromosome 18 in humans and is activated by translocation to the immunoglobulin heavy chain locus on chromosome 14 in more than 80% of B-cell tumours.

ROLE OF DNA REPAIR GENES

- **Cancer can also occur due to mutations in genes that encodes for DNA-repair enzymes.**
- **The product (enzymes) produced by mutated gene is defective hence resulting in defective repair of DNA**

KARYOTYPE IN TUMOUR CELLS

- The most frequent type of structural abnormalities in cancer cells includes
  - 1) balanced translocation,
  - 2) deletions,
  - 3) gene amplification and
  - 4) gain or loss of whole chromosome.

p53 is a Very Important Tumor Suppressor

Most commonly mutated gene in human cancer

"p53 is the Guardian of the Genome"

-Geoff Wahl, the Salk Institute

p53 is Activated in Response to DNA Damage

-p53 is a Transcription Factor for:

-p21 (CKI)
-DNA repair genes
-Apoptotic (Cell Death) genes

In the absence of p53 cells cannot arrest after DNA damage

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AETIOLOGY OF NEOPLASIA

- In majority of cases, the neoplasms are spontaneous in occurrence and the cause is mostly unknown
- However, the aetiologic agents those can cause neoplasia are grouped into three classes
  - **Chemical agents**
  - **Physical agents**
  - **Viruses**
    - DNA viruses
    - RNA viruses

CHEMICALS

- more than **100** are carcinogenic in animals.
- Some chemicals are carcinogenic in some species but not in others
- Different animals have different **P450s** and thus can or cannot turn a given chemical into a true carcinogen
- When one foreign chemical is sufficient to cause cancer, either as a direct or indirect carcinogen, it is said to be **complete**
- When it requires a tumor **promoter** to cause cancer, it is an incomplete carcinogen

- **Promotor** act like a growth Factor on cells that have Already acquired one or more Carcinogenic mutations,

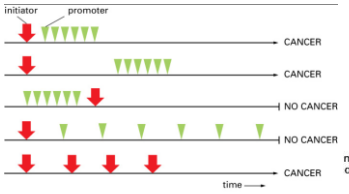

Figure 23–19. Molecular Biology of the Cell, 4th Edition.

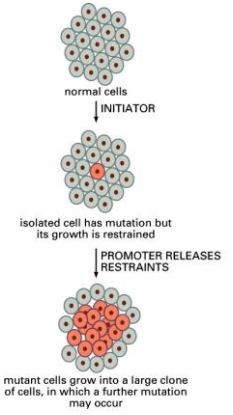

Figure 23–20. Molecular Biology of the Cell, 4th Edition.

- some are **direct** reacting, while others are **indirect** reacting.
- Compounds like N-methyl-N-nitroso Urea are able to react directly with DNA, causing mutations.
- Most chemicals are **pro-carcinogens** (indirect reacting).
- **Liver** is, therefore, frequent target organ
- **Kidney** being the clearing organ is second in line
- All chemicals, have **electron-deficient atoms** and react with electron rich atoms in **RNA**, cellular **proteins** and **DNA**

- Some chemicals are **complete carcinogens**, i.e., they can cause neoplastic transformation after a single dose,
- while others require interaction with other compounds, either carcinogen or promotor.
- Some chemicals **may act in concert** or with other types of carcinogenic influences, e.g., viruses or radiation.
- **Direct reacting** chemicals may include **alkylating agents** (cyclophosphamide etc.,) and **acylating agents** (1-Acetyl-imidazole, Dimethylcarbamyl chloride).
- **Indirect reacting** chemicals may include polycyclic and heterocyclic aromatic **hydrocarbons** (Benzopyrene).

- **Polycyclic hydrocarbons** are present in **fossil fuels and** are produced in the combustion of organic substances, e.g., **benzopyrene** produced in **cigarette** smoke.
- Another class of indirect reacting chemical carcinogen include **aromatic amines** and **azo-dyes**.
- Most of the **aromatic amine** and **azo-dyes** are converted into carcinogens by hepatic **cytochrome-P450 oxygenase system**

Mechanism

- Mutation can occur in any gene, however, **ras** gene mutation is particularly affected in chemical cacrcinogenesis.
- The mutation caused by an **initiator** in the **ras gene** with subsequent action of **promotor** leads to clonal expansion of the mutated cells.
- Such mutated cells require l**ess growth factor** to induce cell proliferation
- **Phorbol ester** (promotor chemical) is a powerful activator of protein kinase C.
- Other **promoter** chemicals includes **hormones, croton oil, phenols** and **drugs**.
- In dogs, it is known that continual stimulation of the mammary gland by progesterone may result in mammary neoplasia.

PHYSICAL AGENTS (RADIATION)

- Certain plastics when implanted in tissues induces sarcomas
- UV light, x-rays and radioactive material can cause cancer
- The occurrence of squamous cell carcinoma in animals due to long exposure to sun light is best example of neoplasia.
- Some breeds of cattle like Hereford Cattle more susceptible to UV light.
- The survivors of the Hiroshima and Nagasaki developed leukaemia after seven years of latency period due to effect of radioactivity.
- Development of **skin cancers** (melanoma, squamous cell carcinoma and basal cell carcinoma) are quite common in humans in **New Zealand** and **Australia**

PHYSICAL AGENTS (RADIATION)

- There are two possible ways by which radiation can cause mutation.
  - First, it can excite local water present in the tissues and thus lead to formation of free radicals which then cause DNA damage.
  - Second, nucleoproteins are probably damaged by radiation, the breaks occur at disulfide bonds.

VIRUSES

- Both DNA and RNA viruses
- **DNA viruses** include **adenovirus, herpesvirus, papovavirus** and **poxvirus**.
- **RNA viruses** include **retrovirus** group those cause neoplasms in animals.
- **DNA viruses** either undergoes proliferation inside the host cell with eventual disruption of the cell or the virus transform the cells but not kill the cell.
- Oncogenic DNA viruses contain **oncogenes**

- **RNA VIRUSES,** reteroviruses have in them an enzyme reverse transcriptase by which they synthesize a DNA copy of their RNA genome.
- This DNA copy of their genome is inserted into the host genome.

Oncogenes Identified from Retroviruses

v-onc	Virus	Host
src	Rous sarcoma virus	Chicken
myc	Avian myelocytomatosis virus	Chicken
erb A, erb B	Avian erythroblastosis virus	Chicken
myb	Avian myeloblastosis virus	Chicken
ets	Avian erythroblastosis virus	Chicken
rel	Avian reticuloendotheliosis virus	Turkey
H-ras	Harvey rat sarcoma virus	Rat
K-ras	Kirsten murine sarcoma virus	Mouse
abl	Abelson murine leukemia virus	Mouse
raf	Murine sarcoma virus	Mouse
fos	Mouse osteosarcoma virus	Mouse
fms	Feline sarcoma virus	Cat
fes	Feline sarcoma virus	Cat
sis	Simian sarcoma virus	Monkey

IMMUNE DEFENCE AGAINST CANCER/NEOPLASIA

Much evidence suggests that host fight against cancer.

TUMOUR ANTIGENS

- **It is quite clear that many tumours have new antigens on cells (tumour) which are not normally found in the same healthy cells.**
- **Tumour antigens are quite diverse.**
- **All may not be immunogenic**

IMMUNOLOGIC SURVEILLANCE (VIGILANCE)

- **There is quite strong evidence that immune response can influence the fate of the neoplasms.**
- **There is clear evidence that immune response prevents development of neoplasia from oncogenic viruses.**
- **The development of the immunity prevents the development and establishment of the neoplastic cells.**

EFFECTOR MECHANISMS IN TUMOUR IMMUNITY

- Cytotoxic T lymphocytes
- Antibody
- Natural killer cells
- Macrophages

Cancer Immuno-surveillance

- Lymphocytes act as sentinel cells (watchmen), recognize and eliminate continuously arising, nascent transformed cells
- Cancer immuno-surveillance appears to be an important host protection process that inhibits carcinogenesis and maintains regular cellular homeostasis

Cancer Immuno-editing

- Immuno-editing is a process by which a person is protected from cancer growth and the development of tumour immunogenicity by their immune system.
- It has three main phases:
  - elimination
  - equilibrium and
  - Escape

- The **elimination** consists of the following four phases:
- **Elimination: Phase 1 (preparatory)**
  - The first phase of elimination involves the initiation of antitumor immune response.
  - Cells of the innate immune system recognize the presence of a growing tumor which has undergone stromal remodeling, causing local tissue damage.
  - This is followed by the induction of inflammatory signals which is essential for recruiting cells of the innate immune system (eg., natural killer cells, natural killer T cells, macrophages and dendritic cells) to the tumor site.
  - During this phase, the infiltrating lymphocytes such as the natural killer cells and natural killer T cells are stimulated to produce IFN-gamma.

- **Elimination: Phase 2 (Cytokines destroy)**
  - In the second phase of elimination, newly synthesised IFN-gamma induces tumor death as well as promoting the production of chemokines (CXCL10, CXCL9 and CXCL11).
  - These chemokines play an important role in promoting tumor death by blocking the formation of new blood vessels.
  - Tumor cell debris produced as a result of tumor death is then ingested by dendritic cells, followed by the migration of these dendritic cells to the draining lymph nodes.
  - The recruitment of more immune cells also occurs and is mediated by the chemokines produced during the inflammatory process.

- **Elimination: Phase 3 (destroyed by apoptosis and ROI)**
  - In the third phase, natural killer cells and macrophages trans-activate one another via the reciprocal production of IFN-gamma and IL-12.
  - This again promotes more tumor killing by these cells via apoptosis and the production of reactive oxygen and nitrogen intermediates.
  - In the draining lymph nodes, tumor-specific dendritic cells trigger the differentiation of Th1 cells which in turn facilitates the development of CD8+ T cells.

- **Elimination: Phase 4 (remaining cells are destroyed)**
  - In the final phase of elimination, tumor-specific CD4+ and CD8+ T cells home to the tumor site and the cytolytic T lymphocytes then destroy the antigen-bearing tumor cells which remain at the site.

There are two pathways for T cell-mediated killing. One makes pores in the target cell to let in secreted proteases.

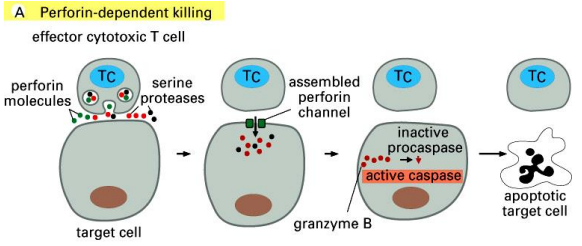

Figure 24–46 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

The second pathway uses an indirect route to activate apoptosis in the target cell.

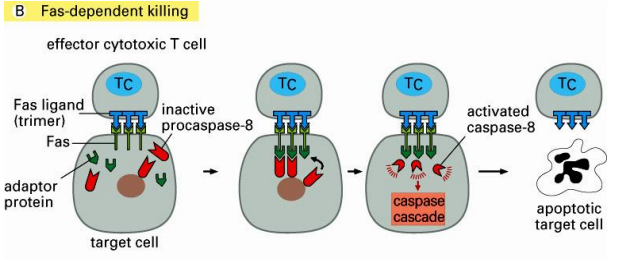

Figure 24–46 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

EQUILIBRIUM AND ESCAPE

- Tumor cell variants which have survived the elimination phase enter the equilibrium phase.
  - In this phase, lymphocytes and IFN-gamma exert a selection pressure on tumor cells which are genetically unstable and rapidly mutating.
- Tumor cell variants which have acquired resistance to elimination then enter the escape phase.
  - In this phase, tumor cells continue to grow and expand in an uncontrolled manner and may eventually lead to malignancies.

POSSIBLE ESCAPE MECHANISMS OF TRANSFORMED CELLS

- Modulation of cell surface antigens occurs in some tumour cells.
- The rapid turnover and shedding of antigens may result in presence of circulating antigens and immune complexes (antigens bound with antibodies)
- It has also been proposed that tumour cells may also produce certain substances which are toxic to the effector cells, suppress the effector cells or destroy antibody.
- Tumour cells may secrete low molecular weight substance that can inhibit chemotaxis of mononuclear cells.
- Another possible escape mechanism is by emergence of cell resistance to immune attack.
- neoplasms progress in situations of immunosuppression

ROLE OF SUPPRESSOR CELLS

- tumour-specific suppressor cells inhibit immune mediated attack on tumour cells.
  - If tumour cells from one mouse are injected into another syngeneic mouse, previously immunized with tumour cells, they will not grow in to tumours.
  - Nevertheless, if along with tumour cells, spleen cells are also injected (taken from the tumour bearing mice) tumour cells will not be rejected.
  - Suppressor cells can also inhibit the cytotoxic reaction.

EFFECTS ON THE HOST

- Space occupying lesion can cause dysfunction of an organ
- Malignant neoplasms, due to having the ability to metastasize, have more serious effects on the host than benign neoplasms.
- Site of neoplasm: Benign neoplasms can also be very dangerous at times, e.g., a benign tumour obstructing the bile duct can cause jaundice and eventually may cause severe liver damage.
  - Similarly, in horses, a benign mass can become twisted around the intestine and thus may cause obstruction or infarction and ultimately death of the horse.
  - Malignant neoplasms may have similar effects on the host but its additional ability to invade and destroy the host tissue has more serious outcomes.

- Neoplasms not only can destroy tissues directly but also by indirect mechanisms which (diseases) are known as paraneoplastic syndromes.
- In cases of benign neoplasms whose cells retain functional characteristics of normal cells and thus can secrete much higher amount of product (secretion) which can cause clinical disease.
- Sometimes, neoplastic cells may secrete hormones or hormone-like substances which they normally do not secrete as, e.g., squamous cell carcinoma of the lung and carcinoma of the mammary gland in dogs may secrete osteoclast activating factor which result in hypercalcaemia.

- Mostly, the significant effect of malignant neoplasms on the host is cachexia and such animals are weak and have generalized wasting.
- Loss of appetite (inadequate food intakes) and/or major sharing of nutrients by the neoplastic mass contribute to the condition.
- The production of TNFα (cachectin) by the activated macrophages stimulated by neoplastic cells, is thought be inhibitor of many of the enzymes of the metabolic process.

MESSAGE

The world witnessed the best medical and health care professionals in the Islamic world during the Middle Ages. The reason of achieving such heights was directly related to teaching of Islam. The HOLLY QUR'AN and the sayings of the Prophet MUHAMMAD (pbH) encouraged the gaining of knowledge. The Prophet MUHAMMAD (pbH) said, "Make use of medical treatment, for ALLAH has not made a disease without appointing a remedy for it, with the exception of one disease, namely old age" [Hadith on Health]. This saying by Prophet motivated the Muslim scientists to find treatment of diseases. The Third Pillar of Islam is that of Charity - to help the poor and sick.

QUESTIONS ???