**Genetics basis in carcinogenesis**

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### Neoplasm #1: Learning objectives

- **Tumor (Latin for swelling)**
  - originally meant all forms of swelling, neoplastic or not.

- **Tumor**: An abnormal growth of tissue.
  - **Tumor** is now considered synonymous with **neoplasm** (Gr., new growth).

- **Neoplasia** (Gr., new growth) is the abnormal proliferation of cells.
  - The growth of the cells exceeds, and uncoordinated with that of the normal tissues.
  - The growth persists in the same excessive manner even after cessation of the stimuli.

- Neoplasms may be
  - benign,
  - pre-malignant or
  - malignant.

### Terminology review:

- **Hypertrophy** - increase in cell size
- **Hyperplasia** – increase in number of cells
- **Metaplasia** – cell type conversion
- **Neoplasia** – abnormal proliferation
- **Dysplasia** – maturation abnormality
- **Anaplasia** – dedifferentiation
- **Desmoplasia** – connective tissue growth
Hypertrophy results from an increase in cell size, while hyperplasia is from an increase in cell number.

**Metaplasia** (Greek: "change in form") is the reversible replacement of one differentiated cell type with another mature differentiated cell type.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Normal</th>
<th>Metaplasia</th>
<th>Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airways</td>
<td>Pseudostratified columnar epithelium</td>
<td>Squamous epithelium</td>
<td>Cigarette smoke</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Transitional epithelium</td>
<td>Squamous epithelium</td>
<td>Bladder stone</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Squamous epithelium</td>
<td>Columnar epithelium</td>
<td>Gastro-esophageal reflux (Barrett’s Esophagus)</td>
</tr>
<tr>
<td>Cervix</td>
<td>Glandular epithelium</td>
<td>Squamous epithelium</td>
<td>Low pH of vagina</td>
</tr>
</tbody>
</table>

Hyperplasia results from an increase in cell number.

Dysplasia (Greek, "malformation"), is a term used in pathology to refer to an abnormality of development. The term dysplasia is typically used when the cellular abnormality is restricted to the originating tissue. Dysplasia is often indicative of an early neoplastic process. Dysplasia, in which cell maturation and differentiation are delayed, can be contrasted with metaplasia, in which cells of one mature, differentiated type are replaced by cells of another mature, differentiated type. Dysplasia is often indicative of an early neoplastic process.

Dysplasia is a term refer to an abnormality of maturation. It is typically used when the cellular abnormality is restricted to the originating tissue. Dysplasia is often indicative of an early neoplastic process.
Anaplastic cells (cancer cells) display marked pleomorphism.

Anaplastic nuclei are variable and bizarre in size and shape.

The nuclei are characteristically extremely hyperchromatic.

The nuclear-cytoplasmic ratio may approach 1:1.

More important, mitoses are often.

They may grow with total loss of communal structures, such as gland formation or stratified squamous architecture.

Anaplasia is the most extreme disturbance in cell growth encountered in the spectrum of cellular proliferations.

Single strands of malignant cells

The malignant cells are arranged in trabecular and solid patterns, with gland formation.

Malignant neoplasms are called cancers. They included:

- Carcinoma in situ (cancer at the site). They do not invade and destroy basement membrane but, given enough time, will transform into invasive cancer.
- Invasive cancers; they invade and destroy the surrounding tissue, may form metastases and eventually kill the host.

Cancer cells can invade and destroy healthy tissues, and they can spread (metastasis) through the bloodstream and the lymphatic system to other parts of the body.

Primary and secondary cancers. Artwork showing the spread of cancer from a primary site in the skin (upper left), through the bloodstream (centre), to form secondary cancers elsewhere in the body (right). The secondary locations shown here are the lungs, liver and a skeletal long bone. The body will produce white blood cells (orange spheres) to attack the cancer cells (purple), but once the cancer has spread (a process called metastasis), the prognosis is poor. Secondary and primary cancers can be treated by surgery and/or radiotherapy and chemotherapy, depending on the location of the tumours.

Laboratory demonstration
Tumors arising from any germ layer or more than ones.

Common presentation of tumor: a painless mass

Distinct tumor border with pseudo-capsule in a benign breast tumor: Fibroaden-oma

Benign tumor of meninges: Meningi-oma

Tumor composes of mammary ducts and fibrous tissue proliferation.

Ectoderm

Neoplasm / Tumor
Pancreatic endocrine tumor: Insulin-oma

Benign tumors, named ending up with – OMA, with exception these tumors are malignant:

- Hepatoma – primary tumor of liver parenchyma
- Lymphoma - primary tumor of lymph node
- Melanoma - tumor of melanocyte
- Seminoma - tumor arising from seminiferous tubule

However in tumors, with their names ending up with – BLASTOMA, they are embryonal cell tumors, and all are malignant tumors, e.g.
- Neuro-blastoma,
- Retino-blastoma and
- Medalo-blastoma.

Cancer: A general name for more than 100 diseases in which abnormal cells grow out of control.

Cancer cells can invade and destroy healthy tissues, and they can spread (metastasis) through the bloodstream and the lymphatic system to other parts of the body.

Malignant tumor of surface epithelium is called 'carcinoma'.

Malignant tumor of connective tissue is called ‘sarcoma’.

Tumors arising from any germ layer or more than ones.

• Colon: Carcinoma
• Muscle: Sarcoma
• Brain: Carcinoma
• Skin, squamous cell carcinoma
• Lung: Bronchogenic carcinoma
• Is it tumor or what!? Is it benign or malignant?

Teratoma: tumor originates from more than one germ-layers
• 80-90%, benign teratoma
• 20-10%, malignant teratoma

Malignant tumor of surface epithelium is called ‘carcinoma’.

Malignant tumor of connective tissue is called ‘sarcoma’.

Malignant tumor of connective tissue is called ‘sarcoma’.

Malignant tumor of surface epithelium is called ‘carcinoma’.

CARCINOMA of COLON

ADENO-CARCINOMA

SARCOMA of MUSCLE / Rhabdomyo-sarcoma

SARCOMA of MUSCLE / Rhabdomyo-sarcoma
• Malignant tumor of connective tissue is called ‘sarcoma’.

SARCOMA of FAT tissue / Lipo-sarcoma

• Most carcinoma METASTASIS via lymphatic and later on vascular routes.

The most common METASTASIS sites: Lungs / Liver

• METASTASIS intra-abdominal tumor: LN / Liver

The most common METASTASIS sites: Lungs / Liver
Carcinogenesis *(the creation of cancer)*, is the process by which normal cells are transformed into cancer cells.

- There are two carcinogenesis pathways.
  - Hyperplasia - Dysplasia - Carcinoma Sequence
    - Adenoma - Carcinoma Sequence
  - Hyperplasia - Dysplasia - Carcinoma Sequence
  - Hyperplasia - Dysplasia - Carcinoma Sequence

Cervix with HPV lesion (cancer related: HPV type 16-18-31)
• Hyperplasia – Dysplasia – Carcinoma Sequence

Natural History of CIN

<table>
<thead>
<tr>
<th></th>
<th>Regress</th>
<th>Persist</th>
<th>Progression to</th>
<th>Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 1</td>
<td>57%</td>
<td>32%</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td>CIN 2</td>
<td>43%</td>
<td>35%</td>
<td>22%</td>
<td>5%</td>
</tr>
<tr>
<td>CIN 3</td>
<td>32%</td>
<td>&lt;56%</td>
<td>&gt;12%</td>
<td></td>
</tr>
</tbody>
</table>


Adenoma - Carcinoma Sequence

CARCINOMA of COLON

Adenoma - carcinoma sequence

adenoma

Adenocarcinoma from pedunculated polyps

Adenocarcinoma from sessile polyps

PRECURSOR LESIONS IN CARCINOMA

Hyperplasia – Dysplasia – Carcinoma Sequence

Adenoma - Carcinoma Sequence
There is a golden period for cancer detection.

Cervix: detect dysplasia by Pap smear
Colon: detect adenoma by endoscope

Neoplasm II: Learning objectives

Carcinogen: Any substance that causes cancer.
Carcinogens anyone?

Regions of Highest Incidence

Geographical cancer incidence variation

Cancer cause: hereditary or environmental factors

Epidemiology: identified environmental risk factors

Annual sunshine (UV radiation)
**Identified risk factors**

- **HPV Infection Increases Risk for Cervical Cancer**
  - High Cervical Cancer Risk
  - Women infected with HPV

- **Combination of Alcohol and Cigarettes Increases Risk for Cancer of the Esophagus**
  - Risk Increase
  - Alcohol drinks consumed per day
  - Cigarettes consumed per day

**Cancer cause: hereditary or environmental factors**

- **Some Viruses or Bacteria**
- **Some Chemicals**
- **Radiation**
- **Heredity**

**Cancer is a preventable disease!!!**

Cancer cause: Lifestyle factors are strongest risk factors

<table>
<thead>
<tr>
<th>Lifestyle Factors</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>35%</td>
</tr>
<tr>
<td>Tobacco use (mainly/inflicted cigarette smoke)</td>
<td>30%</td>
</tr>
<tr>
<td>Reproductive and sexual behavior</td>
<td>7%</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>3%</td>
</tr>
</tbody>
</table>

Other Factors

<table>
<thead>
<tr>
<th>Other Factors</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>10%</td>
</tr>
<tr>
<td>Occupational exposures</td>
<td>4%</td>
</tr>
<tr>
<td>Chemophysical factors (including UV, ionizing radiation)</td>
<td>3%</td>
</tr>
<tr>
<td>Pollution</td>
<td>2%</td>
</tr>
<tr>
<td>Iatrogenic injuries and medical procedures</td>
<td>1%</td>
</tr>
<tr>
<td>Food additives</td>
<td>1%</td>
</tr>
<tr>
<td>Industrial products</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Man speculation cause of cancer...**

- **SQC Ca**

Figure 1.3 The word for “cancer” referring to the medical treatment of a cancer in the Dr. Martin Luther King, Jr. medical center. For a different tool for a cancer, the word is spelled for the medical treatment (SQC) of the disease.
• Cancer etiology: chemical or viral infection?

Tar / skin cancer (Sir P. Pott)  Chick / Sarcoma (P. Rouse)

1775  1911

1977

Dr. Katsushiro Yamagishu

1977-Two-stage carcinogenesis models / @ promoter

1) No Tumors
2) No Tumors
3) Many Tumors
4) No Tumors
5) Many Tumors
6) No Tumors

Symbols: Time -> Initiator Promoter

(1910) Viruses and cancer: From hens to eternity

A year later, Rous published another paper, which took this work a giant step further. He made cell-free filtrates from the tumour using various protocols, and found that they were sufficient to induce tumour growth.

So, a biological agent in the cell-free filtrate could cause tumour development; this agent was subsequently shown to be a virus, and was named after its discoverer as Rous sarcoma virus (RSV).

The importance of this finding was not fully appreciated for some time, and it was only in 1966, at the age of 77, that Rous was awarded the Nobel Prize for this research.

Dr. Francis Peyton Rous (1879-1970), 1966 winner of the Nobel Prize for Medicine for his work viruses that cause cancer in humans. ca 1966
From DNA to DNA sequencing

(1979) First human oncogene

- By the late 1970s, it was well known that retroviral oncogenes could rapidly transform cells, and that the viruses had acquired these genes from the genomes of the mammalian and avian cells that they infected.

- It was therefore proposed that mutations in the cellular homologues of these genes could transform cells in the absence of any viral involvement, and that this occurred in a substantial proportion of human cancers.

- Key discoveries by the Robert Weinberg and Geoffrey Cooper groups showed that such transformation could occur when the DNA of a chemically mutagenized transformed mouse cell was transferred.

- In 1982, not only was the concept of the cellular oncogene confirmed by the cloning of cellular RAS, but the activating mutation was also identified.

- Retinoblastoma (Rb) is a rapidly developing cancer that develops in the cells of retina, the light detecting tissue of the eye.

- In the developed world, Rb has one of the best cure rates of all childhood cancers (95-98%), with more than nine out of every ten sufferers surviving into adulthood.

Mechanism underline oncogenes in tumorigenesis

- DNA Damage
  - Chemical Carcinogens
  - Radiation
  - Infectious Agents

- Point Mutation
- Translocation
- Amplification

Transformation

Retinoblastoma

Leukocoria in a child with retinoblastoma

Squint in a child with retinoblastoma

Heritable retinoblastoma

Fig. 1: In a normal cell (above), a proto-oncogene plays a role in manufacturing proteins that regulate cell growth.
Two-hit theory of Knudson

- Alfred Knudson noted that "what is lacking is direct evidence that cancer can ever arise in as few as two steps and that each step can occur at a rate that is compatible with accepted values for mutation rates".
- Knudson analyzed 48 cases of retinoblastoma with the presence of a family history of the disease. Using Poisson statistics, he showed that the distribution observed was consistent with retinoblastoma being caused by two mutations.
- In familial cases, one hit was inherited whereas the other one was acquired later; in sporadic tumours, both changes were somatic.
- The now famous two-hit hypothesis was, in later years, to merge with the concept of allelic loss of tumour-suppressor genes.

(1953) Two-hit hypothesis

It takes (at least) two to tango

- Children who carry the gene for retinoblastoma on chromosome 13 develop the eye cancer sooner and oftener than those who get it by non-hereditary means. The diagrams at right show why.
- Two-hit theory of Knudson

Proto-oncogene

↓ Mutation

Oncogene

↓ Oncogenic Proteins

Protein Kinase

↓ Cyclins

Cell Cycle

G1 → S phase

Tumor Suppressor Gene

↓ Loss of both Alleles

Standard dogma in molecular carcinogenesis


A decade later Dr. Friend proved it right by identified Rb
Familial adenomatous polyposis coli (FAP) • CRC in familial adenomatous polyposis • Oncogenes and TSGs involvement in FAP • Molecular carcinogenesis in sporadic CRC • Multi-stage molecular carcinogenesis