Genetics basis in carcinogenesis:
Lec 2

Chawalit Pairojkul, KKU, Sep. 2020
Neoplasm II: *Learning objectives*

2.1] Two carcinogenesis pathways
2.2] What causes cancer?
2.3] Genetics basis in carcinogenesis
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

• Cervix with HPV lesion (cancer related: HPV type 16-18-31)
• Squamous cell carcinoma of CERVIX [invasive SQC]

• Hyperplasia – Dysplasia - Carcinoma Sequence
Hyperplasia – Dysplasia – Carcinoma Sequence

- CA in situ: carcinoma in place
- Invasive CA: carcinoma invading beyond basement membrane and can spreading via blood and lymphatic vessels
• Hyperplasia – Dysplasia - Carcinoma Sequence

Normal  Dysplasia / mild  moderate  severe

**Cervical intraepithelial neoplasia (CIN)**

Spectrum of cervical intraepithelial neoplasia: normal squamous epithelium for comparison; CIN I with koilocytic atypia; CIN II with progressive atypia in all layers of the epithelium; CIN III, (carcinoma in situ) with diffuse atypia and loss of maturation.
• Hyperplasia – Dysplasia - Carcinoma Sequence

### Natural History of CIN

<table>
<thead>
<tr>
<th></th>
<th>Regress</th>
<th>Persist</th>
<th>Progression to CIN 3</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>

- Hyperplasia – Dysplasia - Carcinoma Sequence

### Precursor Lesions of Cervical Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>LSIL</th>
<th>HSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>CIN 1, Mild</td>
<td>CIN 3, Carcinoma in situ</td>
</tr>
<tr>
<td></td>
<td>Dysplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CIN 2, Moderate Dysplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CIN 3, Severe Dysplasia</td>
</tr>
</tbody>
</table>

From Figure 6.13, Dehlay RM. The Art and Science of Cytopathology. CD-ROM. ASCP. 1999.

LSIL = Low Grade Squamous Intraepithelial Lesion  
CIN = Cervical Intraepithelial Neoplasia  
HSIL = High Grade Squamous Intraepithelial Lesion
CIN / Cervical Intra-epithelial Neoplasia

Hyperplasia – Dysplasia - Carcinoma Sequence
Adenoma - Carcinoma Sequence:
Malignant tumor arising from a prior benign tumor.
Adenoma - carcinoma sequence

Pedunculated polyps

Sessile polyps

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
• 2.2] What causes cancer?
Carcinogen: *Any substance that causes cancer.*

Carcinogens anyone?
Geographical cancer incidence variation
Cancer cause: hereditary or environmental factors

**Colon cancer**
(Number of new cases per 100,000 people)

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>1</td>
</tr>
<tr>
<td>Japanese families in U.S.</td>
<td>20</td>
</tr>
<tr>
<td>U.S.</td>
<td>50</td>
</tr>
</tbody>
</table>

**Stomach cancer**
(Number of new cases per 100,000 people)

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>70</td>
</tr>
<tr>
<td>Japanese families in U.S.</td>
<td>10</td>
</tr>
<tr>
<td>U.S.</td>
<td>7</td>
</tr>
</tbody>
</table>

**Skin Cancer Incidence**

- **Dallas**: Most
- **Pittsburgh**, **Detroit**: Least

**Annual sunshine (UV radiation)**

- **Least**: Detroit
- **Most**: Dallas
Epidemiology: identified environmental risk factors

**20-Year Lag Time Between Smoking and Lung Cancer**

- **Cigarettes Smoked Per Person Per Year**
  - 1900: 1000
  - 1920: 2000
  - 1940: 3000
  - 1960: 4000
  - 1980: 4000

- **Lung Cancer Deaths (Per 100,000 People)**
  - 1930: 50
  - 1950: 100
  - 1970: 150
  - 1990: 150

**Incidence of Most Cancers**

- 10% of all cancers

### Some Viruses Associated With Human Cancers

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>TYPE of CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr virus</td>
<td>Burkitt's lymphoma</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>Cervical cancer</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Liver cancer</td>
</tr>
<tr>
<td>Human T-cell lymphotrophic virus</td>
<td>Adult T-cell leukemia</td>
</tr>
<tr>
<td>Kaposi's sarcoma-associated herpesvirus</td>
<td>Kaposi's sarcoma</td>
</tr>
</tbody>
</table>

Genetic instructions that cause cancer

Cancer virus
**Identified risk factors**

**HPV Infection Increases Risk for Cervical Cancer**

- **Noninfected women**: Low risk
- **Women infected with HPV**: High risk

**Combination of Alcohol and Cigarettes Increases Risk for Cancer of the Esophagus**

- **Alcoholic drinks consumed per day**:
  - 0
  - 4+
  - 0
  - 4+
- **Packs of cigarettes consumed per day**:
  - 0
  - 0
  - 2+
  - 2+
Cancer cause: hereditary or environmental factors

- Some Viruses or Bacteria
- Some Chemicals
- Radiation

Up to 10% of Breast and Ovarian Cancer Is Hereditary

- Unknown factors
- Known inherited factor
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 inhaled 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>

<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>Geophysical factors (including UV; ionizing radiation)</td>
<td>3%</td>
</tr>
<tr>
<td>Pollution</td>
<td>2%</td>
</tr>
<tr>
<td>Iatrogenic (drugs and medical procedures)</td>
<td>1%</td>
</tr>
<tr>
<td>Food additives</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Industrial products</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
</tr>
</tbody>
</table>
• **Cancer is a preventable disease !!!**
2.3] Genetics basis in carcinogenesis
• Man speculation cause of cancer...

Figure 1.1 The symbol for “tumor” referring to the surgical treatment of cancer in the hieroglyphics of the Edwin Smith papyrus, dated to earlier than 1600 B.C. The reader is referred to Breasted’s translation (1930) of the document for further information.

• SQC Ca
Cancer etiology: chemical or viral infection?

- 1775
  - Tar / skin cancer (Sir P. Pott)

- 1911
  - Chick / Sarcoma (P. Rouse)
Dr Katsusaburo Yamagiwa

1977
1977-Two-stage carcinogenesis models / @ promoter

Symbols: Time → Initiator Promoter
Carcinogenesis: targeting nucleus (genes)

Peyton Rous, 1966

Experiments by John P. Bader at the National Cancer Institute supported the hypothesis that the infection of cells with Rous sarcoma virus requires the synthesis of new viral DNA produced on an RNA template. When the virus is added to cultures of normally dividing cells (a), the cells are transformed into cancer cells.
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

1956

A.Sanger: "Ten years ago, we were happy if we could determine a sequence of 50 nucleotides in a year. Today one can sequence several thousand per day."
• (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.
In a normal cell (above), a proto-oncogene plays a role in manufacturing proteins that regulate cell growth.

Fig 1—Ways by which different oncogene products may disrupt normal regulation of cell growth (after Wyke and Weiss, 1984).

The following are the properties of some oncogene products: growth factor, sis (PDGF); growth factor receptor, erb-b (for EGF); phosphokinases (receptor kinases?), src, fos, jun, abl, yes, ras, mos, raf/mil; GTPase (second messengers?), H, N, K-ras; nuclear proteins, myc, fos, myb, B-lym.
Mechanism underline oncogenes in tumorigenesis
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.
Heretable retinoblastoma
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.

Knudson's insight: eye cancer takes two mutations, not just one, to get started.
• Two-hit theory of Knudson
A decade later Dr. Friend proved it right by identified \textit{Rb}.
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 analysed 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**.
Standard dogma in molecular carcinogenesis

1988

Familial adenomatous polyposis coli (FAP)
• CRC in familial adenomatous polyposis
• Oncogenes and TSGs involvement in FAP

Figure 4. A series of at least five molecular events has been proposed to account for the evolution for
Molecular carcinogenesis in CRCs (left)

Figure 4. A series of at least five molecular events has been proposed to account for the evolution from normal epithelium to carcinoma. These events include:
- LOH and APC Mutation
- Alterations in DNA Methylation
- K-ras Mutation
- LOH and DCC Mutation
- LOH and p53 Mutation

These events occur in a specific order: Dysplasia → Early Adenoma → Intermediate Adenoma → Late Adenoma → Carcinoma.
Right sided colon Ca
• Right-sided colon cancer: PD or mucinous adenocarcinoma
MLH1 & MSH2

The primary genes that can cause the HNPCC syndrome.

ONE in 740.

The average number of people carrying mutations in the genes responsible for HNPCC.
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Mutation Carrier Risk</th>
<th>General Population Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>70-82%</td>
<td>2%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>42-60%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Stomach</td>
<td>13%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>12%</td>
<td>1%</td>
</tr>
<tr>
<td>Kidney/Urinary Tract</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Brain</td>
<td>3.7%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Biliary Tract</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Small Bowell</td>
<td>1-4%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
The cardinal principles of hereditary cancer genetics

Henry Lynch, MD (1928)

1944: US Navy
1945: Professional boxer
1950-60: Psychology, Genetics, Medicine
1961: Medical genetic team
1966: Family cancer
1970: Professor Preventive Medicine Creighton
1984: HNPCC, Lynch syndrome
1996: MLH1, MSH2 (Repair genes)

In 1970, NIH rejected the idea that cancer could be hereditary.
Multi-stage molecular carcinogenesis

- Defects in Terminal Differentiation
- Defects in Growth Control
- Resistance to Cytotoxicity

- Activation of Proto-Oncogenes
- Inactivation of Tumor Suppressor Genes
- Inactivation of Antimetastasis Genes