NEOPLASIA

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(SCBM341- General Pathology: 2017)

Objectives:
After learning, students should be able to describe and discuss in the topics of....

1. Terminology and classification of neoplastic cells
2. Invasion, metastasis, grading, and staging of tumors
3. Cell and molecular biology for cancer development
4. Host defense against tumors
5. Cancer epidemiology

Leading Questions
1. What are characteristics of benign and malignant tumors?
2. How to inhibit cancer cell invasion and metastasis?

Terminology and Classification of Neoplastic cells
Neoplasia means “new growth”

Neoplasm often is referred to as a tumor

The study of tumors is call “oncology”

(oncos = tumor, logos = study of)

Cancer is the common term for all malignant tumors.

(Nature, 2010)

Two basic components of tumor cells
• Proliferating of neoplastic cells (parenchyma)
• Supportive stroma (connective tissue and blood vessels)

Desmoplastic reaction is the process of stroma formation

(Nature, 2010)

Nomenclature of neoplasm or tumor

1. Benign tumor

1.1 Benign tumor of mesenchymal tissue

The suffix “-oma” to the cell of origin
- Fibroblastic cells → Fibroma
- Lipid cells → Lipoma
- Smooth muscle → Leiomyoma

(Pathobiology MU, 2011)
1.2 Benign tumor of epithelial tissue
base on their cells of origin and microscopic architecture

- Adenoma (base on origin cell)
  - Benign epithelial neoplasm that forms glandular patterns.
  - Tumors derived from glands.

- Papilloma (base on microscopic architecture)
  - Benign neoplasm
  - Microscopically visible finger-like projections

- Polyp
  - Neoplasm produces a macroscopically visible projections above a mucosal surface.
  - Polyp preferably is restricted to benign tumor.

2. Malignant tumor

2.1 Malignant tumor of mesenchymal tissue

- They are usually called sarcoma.
- Sarcoma = “fleshy tumor”
  - Fibroblastic cells ➔ Fibrosarcoma
  - Lipid cells ➔ Liposarcoma
  - Smooth muscle ➔ Leiomyosarcoma
2.2 Malignant tumor of *epithelial tissue*

- They are called *carcinoma*.
  - Squamous cell carcinoma (*Squamous cell type*)
  - Adenocarcinoma (*Grandular growth pattern*)

![Image](http://www.glowm.com) ![Image](http://cir.ncc.go.jp)

- Adenocarcinoma
  - *Grandular growth pattern*

- Squamous cell carcinoma
  - *Squamous cell type*

Teratoma (Dermoid cyst)

- It is made up of *variety of parenchymal cell types*.
- Arise from totipotential cells
- Is a benign type

![Image](Robbin, 2010)

Inappropriate nomenclature

Some inappropriate nomenclatures but deeply entrenched usages

- Melanoma = CA of melanocyte
- Seminoma = CA of testicular origin
- Hepatoma = CA of hepatocyte
- Lymphoma = CA of lymphoid tissue
- Leukemia = CA of hematopoietic cells

Dysplasia

- Is a disordered growth, it often occurs in metaplastic epithelium.
- Remains confined by the basement membrane, it is considered to be *a carcinoma in situ*.
- Dysplasia does *not necessarily progress* to cancer.

![Image](Cervical intraepithelial neoplasia, CIN (Robbin, 2005))
Differentiation & Anaplasia

- Well differentiated tumors
  - Cell is resemble normal morphology of original tissue.
  - In general, benign tumors are well differentiated cells.

- Poorly differentiated or undifferentiated tumors
  - This anaplasia is marked by a number of morphologic and functional changes, it is a hallmark of malignant transformation.
  - Lack of differentiation
Anaplasia: a condition of cells in which they have poor cellular differentiation, losing the morphological characteristics of mature cells.

Pleomorphism: variation in size and shape

Hyperchromatic cells are the dark staining of nuclei that contained DNA.

The nuclei are disproportionately large for the cell (nuclear/cytoplasmic ratio = 1:1).

Coarsely clumped chromatin

Increased mitotic figures

The characteristics of malignant cells

Invasion and metastasis

Invasion is the most important sole criterion for malignant tumors.
Metastasis

- The process whereby malignant tumors spread from their site of origin to form other tumors at distant sites.
- Metastasis marks a tumor as malignant.
- Common routes of metastasis include lymphatic channels, blood vessels, and through body cavities.

2. Lymphatic spread
   Most common pathway for carcinoma types

3. Hematogenous spread
   It is typical of sarcoma but is also used by carcinoma.
Characteristics of benign and malignant tumors

Grading of a cancer
- Based on the degree of differentiation of the tumor cells and the number of mitoses
- Presumed correlates of the neoplasm’s aggressiveness
  - Low-grade = the cancer cells tend to be slow-growing, look quite similar to normal cells (are well differentiated), tend to be less aggressive.
  - Intermediate-grade = a middle grade
  - High-grade = the cancer cells tend to be fast growing, look very abnormal (are poorly differentiated), tend to be more aggressive, and are more likely to spread quickly.

The staging of cancer
- Based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of blood-borne metastases
- Two major staging systems are currently in use
  - Union Internationale Contre Cancer (UICC)
  - American Joint Committee (AJC)
**TNM system (UICC)**

T = primary tumor (T1, T2, T3, T4)

N = regional lymph node involvement (N0, N1, N2)

M = metastases (M0, M1 or sometimes M2)

**AJC method system**

Stage 0, I, II, III, IV

**TNM classification:**

- T - primary tumour has grown locally
- N - cancer has spread to the local lymph nodes
- M - cancer has spread to other parts of the body

**Stomach cancer**

- T-1 means the primary tumor is still in the stomach wall. T-3 means the primary tumor has grown right through the stomach wall and T-4 means it is invading nearby structures such as the pancreas.

- N-0 means there is no spread to lymph nodes. N-1 means that some local lymph nodes are affected. N-2 means more extensive spread to local lymph nodes.

- M-0 means there are no metastases. M-1 means that there are metastases to some other area of the body such as the liver or brain.

**Biology of tumor growth**

- Growth of the transformed cells

- The growth rate of tumors correlated with their level of differentiation.

- Most malignant tumors grow rapidly than do benign tumors.
Carcinogenesis is a multistep process in cancer development.

- It results from accumulation of genetic defects.
- 3 stages of carcinogenesis: initiation, promotion, and progression

Molecular basis of cancer

- Targeted genes
  - Proto-oncogenes
  - Tumor suppressor genes
  - Genes controlling apoptosis
  - Genes regulating DNA repair
- Other genes involved
  - Genes regulating angiogenesis
  - Genes enhancing invasion and metastasis

Oncogenes and cancer

- Proto-oncogenes = cellular gene that promote normal growth and differentiation.
- Oncogenes = cancer-causing genes
- Oncoproteins are protein products of oncogenes.
• Oncogenes are derived from protooncogene.

• Oncogenes are promote autonomous cell growth in cancer, their normal cellular counterparts are protooncogenes.

Tumor is a lesion resulting from autonomous abnormal growth of cells that persists after the initiating stimulus has been removed.

Tumor suppressor genes
- Insensitivity to growth
- Inhibitory signals
- Tumor suppressor genes: the protein products that apply brakes to cell proliferation.

A misnomer of “tumor suppressor genes”
- regulate cell growth
- not only to prevent tumor formation

Table 1-1: Selected Tumor Suppressor Genes Involved in Human Neoplasms

<table>
<thead>
<tr>
<th>Subcellular Location</th>
<th>Gene</th>
<th>Function</th>
<th>Tumors Associated with Spontaneous Mutations</th>
<th>Tumors Associated with Inherited Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell surface</td>
<td>TP53</td>
<td>Growth arrest, apoptosis</td>
<td>Carcinomas of skin, breast, lung</td>
<td>Unknown</td>
</tr>
<tr>
<td>Intra-epithelial</td>
<td>p53</td>
<td>Inhibition of MPS, p53 cell-cycle arrest</td>
<td>Neuroblastomas</td>
<td>Neuroblastoma type 1 and neuroectodermias</td>
</tr>
<tr>
<td>Cytoskeleton</td>
<td>BRCA1, BRCA2</td>
<td>Cytoskeletal stability</td>
<td>Schwannomas and meningiomas</td>
<td>Neuroblastoma type 2, von Hippel-Lindau</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>PTEN, STK11</td>
<td>Phosphatase antioxidant</td>
<td>Carcinomas of skin, breast, lung, melanomas</td>
<td>Familial adenomatosis polyposis, colon, endometrial cancers</td>
</tr>
<tr>
<td>Nucleus</td>
<td>p16, p15</td>
<td>Regulation of cell cycle</td>
<td>Retinoblastomas, osteosarcoma</td>
<td>Retinoblastoma, osteosarcoma</td>
</tr>
<tr>
<td>p19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Robbin, 2005)
Tumor angiogenesis

- Angiogenesis is a process of tumors stimulate the growth of host blood vessels (neovascularization).
- It formed for supplying nutrients to the tumor.
- Tumor angiogenesis can occur by recruitment of endothelial cell precursors.

Host defense against tumors
Cytotoxic T lymphocytes (CTLs) are the major immune defense mechanism against tumors.

Normal host cell displaying multiple MHC-associated self antigens

<table>
<thead>
<tr>
<th>Tumor cells expressing different types of tumor antigens</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncogene products: mutated RAS, Bcr/Abl fusion proteins</td>
<td></td>
</tr>
<tr>
<td>Tumor suppressor gene products: mutated p53 protein</td>
<td></td>
</tr>
<tr>
<td>Various mutant proteins in carcinogen, or radiation, induced animal tumors; various mutated proteins in melanomas</td>
<td></td>
</tr>
<tr>
<td>Overexpressed: tyrosinase, gp100, MART in melanomas</td>
<td></td>
</tr>
<tr>
<td>Aberrantly expressed: cancer-testis antigens (MAGE, BAGE)</td>
<td></td>
</tr>
<tr>
<td>Human papilloma virus E6, E7 proteins in cervical carcinoma; EBNA proteins in EBV induced lymphoma</td>
<td></td>
</tr>
</tbody>
</table>

Tumors evade the immune system.

Tumor cell

T cell specific of tumor antigen

T cell recognition of tumor antigen leading to T cell activation

Failure to produce tumor antigen

Antigen-loss variant of tumor cell

Lack of T cell recognition of tumor

Mutation in MHC genes or genes needed for antigen processing

Lack of T cell recognition of tumor

Production of immuno-suppressive proteins

Inhibition of T cell activation

Immuno-suppressive cytokines (e.g., TGF-β)

Cancer epidemiology and prevention

Leading cancer in Thailand (mean annual ASR 2010-2012)

(http://www.nci.go.th/th)
Geographic and environmental factors

Inherited predisposition to cancer

Inherited Cancer Syndromes (Autosomal Dominant)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Inherited Predisposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>RB1</td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>p53</td>
<td>Li-Fraumeni syndrome (various tumors)</td>
</tr>
<tr>
<td>p16INK4A</td>
<td>Melanoma</td>
</tr>
<tr>
<td>APC</td>
<td>Familial adenomatous polyposis/colon cancer</td>
</tr>
<tr>
<td>NF1, NF2</td>
<td>Neurofibromatosis 1 and 2</td>
</tr>
<tr>
<td>BRCA1, BRCA2</td>
<td>Breast and ovarian tumors</td>
</tr>
<tr>
<td>MENT, RET</td>
<td>Multiple endocrine neoplasia 1 and 2</td>
</tr>
<tr>
<td>MSH2, MLH1, MSH6</td>
<td>Hereditary nonpolyposis colon cancer</td>
</tr>
<tr>
<td>PTCH</td>
<td>Nevus basal cell carcinoma syndrome</td>
</tr>
</tbody>
</table>

Familial Cancers

- Familiar clustering of cases, but role of inherited predisposition not clear for each individual
- Breast cancer
- Ovarian cancer
- Pancreatic cancer

Inherited Autosomal Recessive Syndromes of Defective DNA Repair

- Xeroderma pigmentosum
- Ataxia-telangiectasia
- Bloom syndrome
- Fanconi anemia

(Robbins, 2005)
Non hereditary predisposing conditions

- **Chronic inflammation and cancer**
  Ulcerative colitis, Helicobacter pylori gastritis, viral hepatitis, and chronic pancreatitis

- **Precancerous conditions**
  Solar keratosis of the skin, leukoplakia of the oral cavity, vulva, and penis

References