EFFECT OF TUMOR ON HOST

Department of Pathology
Gadjah Mada University School of Medicine

dr. Harijadi

Blok Biomedis, 6 Maret 2009 [12]
EFFECT OF TUMOR ON HOST

Tumors may affect host in several ways

• Immunologic reaction
• Non-immunologic effect
non immunologic effect

CLINICAL FEATURES OF NEOPLASM DEPEND ON

1. Anatomical location
   → morbidity/mortality: i.e. brain tumors → intra-cranial pressure is increasing

2. Local effect
   → pressing surrounding tissue → necrosis, desmoplasia

3. Sistemic effect
   → hormone producing tumor and hormon-like substance
2. Local Effects

- Destruction of surrounding tissue
  - Circulation disturbances
- Growth enlargement → ulcus
- Obstruction of hollow organs
  - Secondary infection
  - Nerve pressure
3. Systemic effect

- Cachexia
- Fever
- Increased BSR
- Anemia
- Decreased body resistance
- Increased tendency of thrombus development
Clinical Manifestations of Malignancy

- Cachexia and wasting
- Endocrine abnormalities
- Paraneoplastic syndromes
Cachexia & wasting

- Origin is complex
- Characterized by weakness, weight loss, anorexia, anemia, infection, and hypermetabolism
- May be mediated in part by cachectin (TNF-α), a product of macrophages that promote catabolism of fatty tissue
Endocrine abnormalities
caused by endocrine gland tumors → hormones → variety of syndromes

A. Pituitary abnormalities:
   1. Prolactinoma → amenorrhea, infertility, galactorrhea
   2. Somatotropin (acidophilic) adenoma → gigantism in children, acromegali in adult
   3. Corticotropin (most often basophilic) adenoma → Cushing disease

B. Adrenocortical abnormalities:
   - adrenogenital syndrome, Conn syndrome, Cushing syndrome (adreno-cortical tumor)

C. Ovarian abnormalities:
   1. Granulosa-theca cell tumor → hyperestrinism
   2. Sertoli-Leydig cell tumor → excess androgen production

D. Trophoblastic tissue abnormalities:
   - mole & choriocarcinoma → excess hCG
Paraneoplastic syndrome

• Symptom complexes in cancer-bearing patients that cannot readily be explained, either by local or distant spread of the tumor or by the elaboration of hormones indigenous to the tissue from which the tumors arose

• **Incidence: 10 % of patients with advance malignancy**
Paraneoplastic syndrome

Important to recognize several problems:

1. Earliest manifestation of occult neoplasm
2. In the patient: may represent significant problems and may even be lethal
3. They may mimic metastatic disease and therefore confound treatment
PARANEOPLASTIC SYNDROMES

ENDOCRINOPATHIES

• **Cushing syndrome:**
  Small cell Ca of lung, pancreatic Ca, neural tumors → ACTH or ACTH-like substance

• **Syndrome of inappropriate ADH secretion:**
  Small cell Ca of lung, intra-cranial neoplasms → ADH or atrial natriuretic hormones

• **Hypercalcemia:**
  Lung SCC, breast Ca, renal Ca, adult T-cell leukemia / lymphoma, ovarian Ca → parathyroid hormone related peptide, TGF- α, TNF- α, IL-1
PARANEOPLASTIC SYNDROMES

ENDOCRINOPATHIES

• **Hypoglycemia:**
  Fibrosarcoma, other sarcoma, LCC → insulin or insulin-like substance

• **Carcinoid syndrome:**
  Bronchial adenoma (carcinoid), pancreatic Ca, gastric Ca → serotonin, bradykinin, histamin (?)

• **Polycythemia:**
  Renal Ca, cerebellar hemangioma, LCC → erythropoietin
PARANEOPLASTIC SYNDROMES

Nerve and muscle syndromes
• Myasthenia: bronchogenic Ca → immunologic
• Disorders of the central & peripheral nervous system: breast Ca → immunologic

Dermatologic disorders
• Acanthosis nigricans: gastric Ca, lung Ca, uterine Ca
• Dermatomyositis: bronchogenic Ca, breast Ca → immunologic (?)

Osseous, articular, and soft tissue changes
• Hypertrophic osteoarthropathy and clubbing of the fingers: bronchogenic Ca → ?
Vascular and hematologic changes

- Venous thrombosis (Trousseau phenomenon): pancreatic Ca, bronchogenic Ca, other cancers → tumor products (mucin that activate clotting)
- Nonbacterial thrombotic endocarditis: advanced cancers → hypercoagulability
- Anemia: thymic neoplasm → ? (unknown)

Others

- Nephrotic syndrome: various cancers → tumor antigen, immune complexes
Tumor Immunology

immunologic effect
TUMOR IMMUNITY

Normal cell

Genetic alteration

Neoplastic transformation

Expression of surface antigens

Non-self antigen

Induce tumor surveillance
Questions:
1. What is the nature of tumor antigens
2. What host effector systems may recognize tumor cells
3. Is antitumor immunity effective against spontaneous neoplasms
4. Can immune reactions against tumors be exploited for immunotherapy
Tumor antigen

Tumor antigenicity is usually assessed by:

• The ability of an animal to resist a live tumor implant after previous immunization with live or killed tumor cells

• The ability of tumor free host animals to resist challenge when infused with sensitized T cells from a tumor-immunized syngeneic donor

• The demonstration in vitro of tumor cells destruction by cytotoxic CD8+ T cells derived from a tumor-immunized animal
Tumor antigen

Two broad categories:

**TSAs** (Tumor Spesific Antigens)

**TAAs** (Tissue Associated Antigens)
**Tumor antigens**

**TSAs (Tumor Specific Antigens)**
- Present only on tumor cells not on any normal cells
- Derived from peptides that are uniquely present within tumor cells and presented on the cell surface by class I MHC molecules → evoke a cytotoxic cell response

**TAAs (Tissue Associated Antigens)**
- Present on tumor cells and also on some normal cells
Tumor antigen

TSA (Tumor Spesific Antigen)
- Tissue-specific shared antigen
- Antigen resulting from mutation
- Viral antigen

TAA (Tissue Associated Antigen)
- Tissue specific antigen
- Overexpressed antigen
- Oncofetal antigen
- Differentiation antigen
Tissue-specific shared antigen

Encoded by genes that are silent in virtually all normal adult tissues but expressed in a number of tumors of various histologic types

**Testis:** the only normal organ in which MAGE protein are present → cannot be expressed on their cell surface
Antigen resulting from mutation

- Mutated protooncogene and tumor suppressor gene
- P53, K-ras, CDK4, bcr-c-abl
Viral antigens

- Antigens derived from oncogenic viruses
- E7 protein of HPV-16
Tissue specific antigen

- Shared by tumor cells and their normal untransformed counterparts
- Melanocytes and melanoma cells both express tyrosinase
D. Overexpressed antigen

- C-erbB2 (neu): overexpressed in 30% of breast and ovarian cancer
Oncofetal antigens

- Normally expressed in embryonic tissue
- AFP: Alpha Fetoprotein
- CEA: Carcinoembryonic antigen
Differentiation antigen

- Peculiar to the differentiation state at which cancer cells are arrested
- CD10 (CALLA antigen – expressed by early B cell, B-cell lymphoma and leukemia)
- PSA (Prostate Specific Antigen)
- $\beta$-hCG
<table>
<thead>
<tr>
<th>Normal host cell displaying multiple MHC-associated self antigens</th>
<th>Tumor cells expressing different types of tumor antigens</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Normal cell with self proteins" /></td>
<td><img src="image2" alt="Tumor cell with self protein" /></td>
<td><strong>Oncogene products:</strong> mutated RAS, Bcr/Abl fusion proteins; Tumor suppressor gene products: mutated p53 protein</td>
</tr>
<tr>
<td><img src="image3" alt="Normal cell with self proteins" /></td>
<td><img src="image4" alt="Tumor cell with self protein" /></td>
<td>Various mutant proteins in carcinogen, or radiation, induced animal tumors; various mutated proteins in melanomas</td>
</tr>
<tr>
<td><img src="image5" alt="Normal cell with self proteins" /></td>
<td><img src="image6" alt="Tumor cell with self protein" /></td>
<td>Overexpressed: tyrosinase, gp100, MART in melanomas; Aberrantly expressed: cancer-testis antigens (MAGE, BAGE)</td>
</tr>
<tr>
<td><img src="image7" alt="Normal cell with self proteins" /></td>
<td><img src="image8" alt="Tumor cell with self protein" /></td>
<td>Human papilloma virus E6, E7 proteins in cervical carcinoma; EBNA proteins in EBV induced lymphoma</td>
</tr>
</tbody>
</table>
Cellular effectors that mediate immunity

Cytotoxic T lymphocytes
• Protective role against virus-associated tumors EBV, HPV (possessing MHC class 1)

Natural killer cells (NK cells)
• Lymphocytes capable of destroying tumor cells without prior sensitization (after activation with IL-2), including many that appear non-immunogenic for T cells

Macrophages
ADCC
Antitumor Effector Mechanisms
**IMMUNOSURVEILLANCE**

**Facts:**

Increased occurrence of tumors
In immunodeficient host

→

Immunosurveillance

*(it is not perfect)*
Mechanisms to escape from Tumor Immunosurveillance

1. Selective outgrowth of antigen-negative variants
2. Loss or reduced expression of histo-compatibility antigens
3. Lack of co-stimulation
4. Immunosuppression
   - oncogenic agent: ionizing radiation, chemicals
   - tumor product: TGF-β
   - immune response induced by tumor cells → activation of suppressor T cells
5. Apoptosis of cytotoxic T cells
**Anti-tumor immunity**

- Tumor cell
- Tumor antigen
- MHC molecule
- T cell specific for 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

**Immune evasion by tumors**

- Mutations in MHC genes or genes needed for antigen processing
- Class I MHC-deficient tumor cell
- Lack of T cell recognition of tumor

**Production of immuno-suppressive proteins**

- Immunosuppressive cytokines (e.g., TGF-β)
- Inhibition of T cell activation
## Tumor Marker

<table>
<thead>
<tr>
<th>Marker</th>
<th>Associated Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormones</strong></td>
<td><strong>Trophoblastic tumor and testicular non-seminoma</strong></td>
</tr>
<tr>
<td><strong>HCG</strong></td>
<td><strong>Medullary thyroid carcinoma (MTC)</strong></td>
</tr>
<tr>
<td><strong>Calcitonin</strong></td>
<td><strong>Phaeochromocytoma and associated tumors</strong></td>
</tr>
<tr>
<td><strong>Catecholamin and metabolit</strong></td>
<td><strong>Paraneoplastic syndrome</strong></td>
</tr>
<tr>
<td><strong>Ectopic hormone</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Oncofetal antigen</strong></td>
<td><strong>HCC, non seminomatous testicular germ cell tumor</strong></td>
</tr>
<tr>
<td><strong>Alfa-fetoprotein (AFP)</strong></td>
<td><strong>Colon, pancreas, lung, gaster, breast carcinoma</strong></td>
</tr>
<tr>
<td><strong>CEA</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Isoenzim</strong></td>
<td><strong>Prostatic carcinoma</strong></td>
</tr>
<tr>
<td><strong>Prostatic Acid Phosphatase</strong></td>
<td><strong>Small cell lung Ca, neuroblastoma</strong></td>
</tr>
<tr>
<td><strong>Neuron specific enolase (NSE)</strong></td>
<td><strong>Multipel myeloma and other gammopathy</strong></td>
</tr>
<tr>
<td><strong>Specifc protein</strong></td>
<td><strong>Ovarian carcinoma</strong></td>
</tr>
<tr>
<td><strong>Imunoglobulin</strong></td>
<td><strong>Colon, pancreas carcinoma</strong></td>
</tr>
<tr>
<td><strong>PSA</strong></td>
<td><strong>Breast carcinoma</strong></td>
</tr>
<tr>
<td><strong>Mucin &amp; other glicoprotein</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CA-125</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CA-19-9</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CA-15-3</strong></td>
<td></td>
</tr>
</tbody>
</table>