Host/Tumor Relationships

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Host/Tumor Relationships - Lecture Outline

• Paraneoplastic syndromes
• Cancer as a “Nitrogen Trap”
• Hypoglycemia
• Anorexia and Cachexia
• Angiogenesis
• Hypercalcemia
• Hematologic effects
• Changes in Circulating Protein
• Immune response
• Hormone production by neoplasms
• Hormone dependence of some tumors
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<th>Major Forms of Underlying Cancer</th>
<th>Causal Mechanism</th>
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<td><strong>Endocrinopathies</strong></td>
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<tr>
<td>Cushing syndrome</td>
<td>Small cell carcinoma of lung&lt;br&gt;Pancreatic carcinoma&lt;br&gt;Neural tumors</td>
<td>ACTH or ACTH-like substance</td>
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<tr>
<td>Syndrome of inappropriate antidiuretic hormone secretion</td>
<td>Small cell carcinoma of lung; intracranial neoplasms&lt;br&gt;Brain carcinoma&lt;br&gt;Renal carcinoma&lt;br&gt;Adult T-cell leukemia/lymphoma</td>
<td>Antidiuretic hormone or atrial natriuretic hormones</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Squamous cell carcinoma of lung&lt;br&gt;Breast carcinoma&lt;br&gt;Renal carcinoma&lt;br&gt;Adult T-cell leukemia/lymphoma&lt;br&gt;Ovarian carcinoma</td>
<td>Parathyroid hormone–related protein (PTHrP), TGF-α, TNF, IL-1</td>
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<tr>
<td>Hypoglycemia</td>
<td>Fibrosarcoma&lt;br&gt;Other mesenchymal sarcomas&lt;br&gt;Hepatocellular carcinoma</td>
<td>Insulin or insulin-like substance</td>
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<td>Carcinoid syndrome</td>
<td>Bronchial adenoma (carcinoid)&lt;br&gt;Pancreatic carcinoma&lt;br&gt;Gastric carcinoma</td>
<td>Serotonin, bradykinin</td>
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<td>Polycythemia</td>
<td>Renal carcinoma&lt;br&gt;Cerebellar hemangioma&lt;br&gt;Hepatocellular carcinoma</td>
<td>Erythropoietin</td>
</tr>
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<td><strong>Nerve and Muscle Syndromes</strong></td>
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<tr>
<td>Myasthenia</td>
<td>Bronchogenic carcinoma</td>
<td>Immunologic</td>
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<td>Disorders of the central and peripheral nervous systems</td>
<td>Breast carcinoma</td>
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<td><strong>Dermatologic Disorders</strong></td>
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<tr>
<td>Acanthosis nigricans</td>
<td>Gastric carcinoma&lt;br&gt;Lung carcinoma&lt;br&gt;Uterine carcinoma</td>
<td>Immunologic; secretion of epidermal growth factor</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Bronchogenic, breast carcinoma</td>
<td>Immunologic</td>
</tr>
<tr>
<td><strong>Osseous, Articular, and Soft Tissue Changes</strong></td>
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<tr>
<td>Hypertrophic osteoarthropathy and clubbing of the fingers</td>
<td>Bronchogenic carcinoma</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Vascular and Hematologic Changes</strong></td>
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<tr>
<td>Venous thrombosis (Trousseau phenomenon)</td>
<td>Pancreatic carcinoma&lt;br&gt;Bronchogenic carcinoma&lt;br&gt;Other cancers</td>
<td>Tumor products (mucins that activate clotting)</td>
</tr>
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<td>Nonbacterial thrombotic endocarditis</td>
<td>Advanced cancers</td>
<td>Hypercoagulability</td>
</tr>
<tr>
<td>Anemia</td>
<td>Thymic neoplasms</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
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<tr>
<td>Nephrotic syndrome</td>
<td>Various cancers</td>
<td>Tumor antigens, immune complexes</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone; TGF, transforming growth factor; TNF, tumor necrosis factor; IL, interleukin.
1. Cancer as a “Nitrogen Trap”

Malignant tumors continue to grow during starvation of the host and in advanced cancer there is a loss of host tissue mass. The underlying factors have not been clearly delineated but increased uptake of amino acids and decreased protein and amino acid catabolism are probably important factors.
2. Hypoglycemia

Although hypoglycemia does not occur in the majority of cancer patients, it is a frequent finding. It is seen, for example, in 50% of patients with large fibrosarcomas and in 30% of patients with hepatomas. When hypoglycemia occurs it may be caused by one or more of the following factors:

a. Anorexia

b. Insulinoma. Tumors of the beta cells in the pancreas may produce large amounts of insulin which will cause hypoglycemia. Ectopic production of insulin by tumors of other tissues can have the same effect.

c. Hepatic glucose underproduction. Hepatomas have diminished activities of gluconeogenic enzymes and they can disrupt liver function. Metastases in the liver also impair normal liver metabolism.

d. Glucose consumption by tumors. Tumors tend to have high rates of glycolysis.
Anorexia and Cachexia

Anorexia is a major contributor to cachexia in cancer. Other factors contributing to cachexia are nausea, obstruction of the gastro-intestinal tract, malabsorption, hemorrhage, necrosis, ulcerations, proteinuria, tumor necrosis factor (TNF$\alpha$), interferon-$\gamma$, interleukin–6 and infections. The weight loss may be the first symptom noted. In other cases weight loss can be observed with advancing cancer even with adequate food intake. An increase in basal metabolic rate is a common finding in patients with advanced cancer.

Figure 2 | Cori cycle with sources of gluconeogenic substrates. Tumours produce factors such as lipid-mobilizing factor (LMF), which induces breakdown of adipose tissue into fatty acids, and proteolysis-inducing factor (PIF), which induces protein degradation (amino acids) in skeletal muscle. Tumour necrosis factor (TNF)-α also contributes to these processes. These are important gluconeogenic substrates that can be used in acute-phase protein (APP) synthesis by the liver. Tumours convert glucose to lactate, which is transferred to the liver, where it is converted back into glucose. This cycle uses a large amount of energy, and might contribute to cachexia.
4. Angiogenesis

Folkman and others have noted that unless a tumor elicits new blood vessels it will not exceed a 2 mm diameter. Substances that are released by the tumor and promote vascularization are termed angiogenic factors. These include aFGF, basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), angiogenin, TGF-alpha, TGF-beta and TNF-alpha. Substances under investigation as anti-angiogenic factors include three groups:

1. metaloproteinase inhibitors
2. Inhibitors of endothelial cell function including endostatin and thalidomide
3. agents that target angiogenic factors including antibodies and inhibitors of the receptors of factors such as VEGF, bFGF and PDGF. Bevacizumab (Avastin) targets VEGF and has been approved for treatment of colon cancer.

Balancing the angiogenic switch

- **Activators**
  - VEGF-A
  - VEGF-B, -C
  - FGF1 (aFGF)
  - FGF2 (bFGF)
  - Other FGFs etc.

- **Inhibitors**
  - Thrombospondin-1, -2
  - Interferon α/β
  - Angiostatin
  - Endostatin
  - Collagen IV fragments etc.

*Figure 13-46 The Biology of Cancer (© Garland Science 2007)*
Signaling pathways activated by VEGF. VEGF regulates several endothelial cell functions, including proliferation, differentiation, permeability, vascular tone, and the production of vasoactive molecules. Upon ligand binding, the receptor tyrosines are phosphorylated, allowing the receptor to associate with and activate a range of signaling molecules, including phosphatidylinositol 3-kinase (PI_3K), Shc, Grb2, and the phosphatases SHP-1 and SHP-2. VEGF receptor activation can induce activation of the MAPK cascade via Raf stimulation leading to gene expression and cell proliferation, activation of PI_3K leading to PK3 activation and cell survival, activation of PLC-γ leading to cell proliferation, vasopermeability, and angiogenesis.
5. Hypercalcemia

Bone pain, hypercalcemia and osteolytic lesions occur frequently in patients with a wide variety of types of cancer. The hypercalcemia can occur without direct metastasis to the bone. There may be ectopic release of parathyroid hormone (PTH) or tumor production of osteolytic substances including prostaglandins, osteoclast-stimulating substance and parathyroid hormone-related protein (PTHrP). The latter is believed to be the most important factor.

The production of DKK1, an inhibitor of osteoblast differentiation, by myeloma cells is associated with the presence of lytic bone lesions in patients with multiple myeloma.

6. Hematologic effects

Cancer can be associated with anemia, leukopenia, hemorrhage and sometimes hypercoagulability. Increased blood clotting may be caused by the synthesis of tissue factor by cancer cells.
7. Changes in circulating proteins

There may be increased levels of enzymes and other proteins in plasma which are released from tumors. Examples are acid phosphatase and prostate specific antigen (PSA) in prostate cancer and carcinoembryonic antigen in colon cancer. Alpha-fetoprotein can be an indicator of hepatoma. Human chorionic gonadotropin (HCG) levels are elevated in choriocarcinoma and testicular germ cell tumors.

Multiple myeloma is a multifocal osteolytic neoplasm of bone marrow. Myeloma patients have cells of clonal origin which produce a single immunoglobulin (IgG, IgA, IgD or IgE). The immunoglobulin may accumulate in the blood at levels ten times or more higher than all the natural immunoglobulins. In about a third of such patients, the light chains are synthesized in excess and considerable amounts may appear in the urine. The light chains in the urine have been named Bence-Jones proteins after the London physician who described them in 1840. Bence-Jones proteins precipitate at 60°C but redissolve at 100°C.
8. Immune response

An impaired immune response is frequently seen in cancer patients. Patients with early and slowly progressing forms of cancer are less severely affected. Cell mediated immunity is affected first. Later, humoral function also becomes depressed. For most patients immune impairment is believed to be a consequence rather than a cause of the disease. An impaired response occurs with a wide range of tumors including solid tumors. Tumors sometimes exhibit tumor-specific antigens. There are several mechanisms by which tumors may escape immune surveillance:

a. the tumor antigen may be too weak quantitatively or qualitatively
b. there may be drug-induced immune suppression
c. antigen shedding can occur
d. tumor antigens may be coated by sialomucins
e. tumor growth may be too fast and the tumors serve as an immunological sink.
<table>
<thead>
<tr>
<th>Strategy</th>
<th>Mechanism</th>
<th>Agent being evaded</th>
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<tbody>
<tr>
<td>Hide identity</td>
<td>repress tumor antigens (TATA or TSTA), repress MHC class I proteins</td>
<td>cytotoxic T lymphocytes</td>
</tr>
<tr>
<td>Hide stress</td>
<td>repress NKG2D ligands (e.g., MICA)</td>
<td>NK cells</td>
</tr>
<tr>
<td>Inactivate immunocytes</td>
<td>destroy immunocyte receptors</td>
<td>NK cells; cytotoxic T lymphocytes</td>
</tr>
<tr>
<td></td>
<td>saturate immunocyte receptors with adenosine, MICA</td>
<td>NK cells; variety of immunocytes</td>
</tr>
<tr>
<td>Avoid apoptosis</td>
<td>inhibit caspase cascade by increasing IAPs, acquire resistance to FasL-mediated apoptosis</td>
<td></td>
</tr>
<tr>
<td>Induce immunocyte apoptosis</td>
<td>release soluble FasL, release cytokines (IL-10, TGF-β)</td>
<td>cytotoxic T lymphocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cytotoxic T lymphocytes, dendritic cells, macrophages</td>
</tr>
<tr>
<td>Neutralize intracellular toxins</td>
<td>enzymatic detoxification of H₂O₂, prostaglandin E₂</td>
<td>macrophages, NK cells</td>
</tr>
<tr>
<td>Neutralize complement</td>
<td>overexpress mCRPs</td>
<td>complement system</td>
</tr>
</tbody>
</table>

Table 15-3 The Biology of Cancer (© Garland Science 2007)
Paraneoplastic neurological degenerations are rare conditions that affect about 1 in 10000 patients with cancer. In two thirds of patients with paraneoplastic neurological degeneration the diagnosis of the neurological disorder precedes the diagnosis of cancer.

About half the patients with paraneoplastic neurological disorders die from the cancer and about half die from the neurological disorder.

Paraneoplastic neurological degenerations (PNDs) are triggered by an immune response against neuronal antigens that are expressed in cancer cells. The response is characterized by the presence of PND antigen-specific CD8+ killer cells in the blood of patients.

9. Hormone production by neoplasms

When cancer occurs in endocrine glands the ability of the cells to produce hormones may sometimes be lost but when it is retained a pathological over-production of hormone can occur. In such cases it is the endocrine abnormality which will draw attention to the tumor. Examples are

a. acromegaly from a pituitary tumor producing growth hormone
b. Cushing's disease either from a pituitary tumor producing ACTH or less commonly from an adrenal tumor
c. hypertension from catecholamines produced by a pheochromocytoma
d. hypoglycemia from insulin produced by an insulinoma.

The hormone may be inappropriate as in virilizing ovarian tumors or tumors causing precocious sexual development in young males. There can also be ectopic hormone production by non-endocrine tumors such as ACTH production by some lung tumors.
10. Hormone dependence of some tumors

The first demonstration of tumor regression after endocrine deprivation was provided by Beatson in 1896. Ovariectomy of two women had a beneficial effect on breast cancer. In some cases breast cancer is supported by estrogens produced by the adrenal gland and in these cases adrenalectomy may result in prolonged regression of breast cancer. Ovariectomy is of benefit to about 20-30% of women who are premenopausal but is not usually beneficial after menopause. Response correlates with the retention of estrogen receptors in the breast cancer.

A medical rather than surgical approach is currently used with the anti-estrogen, tamoxifen. Inhibition of adrenal conversion of cholesterol to steroid hormones can be achieved with aminogluthethimide which can be given together with a replacement corticosteroid. Huggins showed that castration or estrogen administration could cause regression of prostate cancer.
Suggested Reading

- Angiogenesis: Chapter 13
- Calcium Metabolism: pages 638-643
- Immunology: Chapter 15