Lecture 7: Biochemistry of cancer and tumor markers

**Biochemistry of Cancer and Tumor Markers**

The term cancer applies to a group of diseases in which cells grow abnormally and form a malignant tumor. It is a long term multistage genetic process. The first stage is when the DNA is damaged by some form of carcinogen: physical, chemical, and biologic agents (e.g. smoking, radiation, chemicals, and virus). These agents damage or alter DNA, so that cancer is truly a disease of the genome. At some later time, additional damage occurs that eventually leads to chromosome breakdown and rearrangement. This process produces a new phenotype that loses control over the process of mitosis. The process of mitosis continues and unlimitedly produces malignant tumor cells.

Eventually, there is a production of a growing mutant cell that expresses oncogenes. Oncogenes are mutated derivatives of normal genes (proto-oncogenes) whose function is to promote proliferation or cell survival. (Oncogenes: are genes capable of inducing or maintaining transformation of cells). Benign tumor cells have lost growth control but do not metastasize.

Much current interest in cancer is focused on the study of oncogenes and tumor suppressor genes. Normal cells contain potential precursors of oncogenes, designated proto-oncogenes. Activation of these genes to oncogenes is achieved by at least five mechanisms:

1. promoter and enhancer insertion
2. Chromosomal translocation
3. gene amplification
4. Point mutation

Activated oncogenes influence cellular growth by perturbing normal cellular mechanism of growth control, by acting as growth factors or receptors, and probably by other means as well.
Lecture 7: Biochemistry of cancer and tumor markers

Tumor suppressor genes (normal growth suppressor genes) encode proteins that inhibit proliferation, promote cell death, or repair DNA; both alleles need to be inactivated for transformation (a loss of function). Growth suppressor genes have been called the guardians of the cell. Tumor suppressor genes are now recognized as key players in the genesis of cancer. Important tumor suppressor genes include RB1 and P53, both of which are nuclear phosphoproteins and probably affect the transcription of genes involved in regulating events in the cell cycle.

Tumor progression reflects instability of the tumor genome probably due at least in part to defects in DNA repair systems, activation of additional oncogenes, and inactivation of additional tumor suppressor genes. The extensive biochemical analyses of the Morris minimal-deviation Hepatomas (tumors originally induced in rats by feeding them the carcinogens fluorenylphthalamic acid, fluorenylacetamide compounds, or trimethylaniline. These hepatocellular carcinomas are transplantable in an inbred host strain of rats and have a variety of growth rates and degrees of differentiation. All these tumors are malignant and eventually kill the host. The term “minimal deviation” was coined by Potter to convey the idea that some of these neoplasms differ only slightly from normal hepatic parenchymal cells) led Weber to formulate the “molecular correlation concept” of cancer, which states that “the biochemical strategy of the genome in neoplasia could be identified by elucidation of the pattern of gene expression as revealed in the activity, concentration, and isozyme aspects of key enzymes and their linking with neoplastic transformation and progression.” Weber proposed three general types of biochemical alterations associated with malignancy:

1. transformation-linked alterations that correlate with the events of malignant transformation and that are probably altered in the same direction in all malignant cells;
2. progression-linked alterations that correlate with tumor growth rate, invasiveness, and metastatic potential; and
3. coincidental alterations that are secondary events and do not correlate strictly with transformation or progression.
Lecture 7: Biochemistry of cancer and tumor markers

Those metabolic pathways that contained enzymes which fulfilled one or more of these criteria are indicated in Table (1) along with the alteration that was observed in cancer.

**Table(1) Molecular Correlation Concept and Affected Processes**

<table>
<thead>
<tr>
<th>Biochemical Process</th>
<th>Alteration in Cancer Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrimidine and purine synthesis</td>
<td>Increased</td>
</tr>
<tr>
<td>Pyrimidine and purine catabolism</td>
<td>Decreased</td>
</tr>
<tr>
<td>RNA and DNA synthesis</td>
<td>Increased</td>
</tr>
<tr>
<td>Glucose catabolism</td>
<td>Decreased</td>
</tr>
<tr>
<td>Glucose synthesis</td>
<td>Increased</td>
</tr>
<tr>
<td>Amino acid catabolism (for gluconeogenesis)</td>
<td>Decreased</td>
</tr>
<tr>
<td>Urea cycle</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

**Enzymes in Malignancy**

Plasma total enzyme activities may be raised or an abnormal isoenzyme detected, in several neoplastic disorders.

- Serum prostatic (tartrate-labile) acid phosphatase activity rises in some cases of malignancy of the prostate gland.

- Any malignancy may be associated with a non-specific increase in plasma LD$_1$ (HBD) and, occasionally, transaminase activity.

- Plasma transaminase and alkaline phosphatase estimations may be of value to monitor treatment of malignant disease. Raised levels may indicate secondary deposits in liver or of alkaline phosphatase, in bone. Liver deposits may also cause an increase in plasma LD or GGT.

- Tumors occasionally produce a number of enzymes, such as the 'Regan' ALP isoenzyme, LD (HBD) or CK-BB. assays of which may be used as an aid to diagnosis or for monitoring treatment.

A number of oncodevelopmental tumor-associated antigens appear on tumor cells as a result of the apparent re-expression (or increased expression) of embryonic genes, and a number of these are useful as tumor markers for cancer diagnosis and disease progression.

These include alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and a number of inappropriately (ectopically) produced hormones. (Table (2)).
Classification of Tumor Markers

Tumor markers come from a variety of groups:

- Enzymes, glycoproteins, hormones and hormone-like substances, hormone receptors, oncogenes, and oneogene reseptors. The list of tumor markers that arise from this list is quite extensive. However, because of the low sensitivity and specificity of most tumor markers, the Food and Drug Administration (FDA) has approved only a few assay kits as tumor markers.

What are they?

Tumor markers are substances, usually proteins that are produced by the body in response to cancer growth or by the cancer tissue itself. Some tumor markers are specific, while others are seen in several cancer types. Many of the well-known markers are also seen in non-cancerous conditions. Consequently, these tumor markers are not diagnostic for cancer.

There are only a handful of well-established tumor markers that are being routinely used by physicians. Many other potential markers are still being researched. Some marker tests cause great excitement when they are first discovered but, upon further investigation, prove to be no more useful than markers already in use.

The goal is to be able to screen for and diagnose cancer early, when it is the most treatable and before it has had a chance to grow and spread. So far, the only tumor marker to gain wide acceptance as a general screen is the Prostate Specific Antigen (PSA) for men. Other markers are either not specific enough (too many false
Lecture 7: Biochemistry of cancer and tumor markers

positives, leading to expensive and unnecessary follow-up testing) or they are not elevated early enough in the disease process.

Some people are at a higher risk for particular cancers because they have inherited a genetic mutation. While not considered tumor makers, there are tests that look for these mutations in order to estimate the risk of developing a particular type of cancer. BRCA1 and BRCA2 are examples of gene mutations related to an inherited risk of breast cancer and ovarian cancer.

Why are they done?
Tumor markers are not diagnostic in themselves. A definitive diagnosis of cancer is made by looking at biopsy specimens (e.g., of tissue) under a microscope. However, tumor markers provide information that can be used to:

Screen: Most markers are not suited for general screening, but some may be used in those with a strong family history of a particular cancer. In the case of genetic markers, they may be used to help predict risk in family members. (PSA testing for prostate cancer is an example).

Help diagnose: In a patient that has symptoms, tumor markers may be used to help identify the source of the cancer, such as CA-125 for ovarian cancer, and to help differentiate it from other conditions.

Determine prognosis. Some tumor markers can be used to help doctors determine how aggressive a cancer is likely to be.

Guide Treatment. Some tumor markers will give doctors information about what treatments their patients may respond to.

Monitor Treatment. Tumor markers can be used to monitor the effectiveness of treatment, especially in advanced cancers. If the marker level drops, the treatment is working; if it stays elevated, adjustments are needed.

Determine recurrence. Currently, one of the biggest uses for tumor markers is to monitor for cancer recurrence. If a tumor marker is elevated before treatment, low after treatment, and then begins to rise over time, then it is likely that the cancer is returning. (If it remains elevated after surgery, then chances are that not all of the cancer was removed.)
Lecture 7: Biochemistry of cancer and tumor markers

- **LUNG**
  - CK-BB, CEA (2)
  - CA 15–3, CA 549

- **HEPATOCELLULAR**
  - CA 19–9, AFP (1, 4)
  - Alk. Phos., LDH

- **PROSTATE**
  - PSA (1, 2, 4)
  - PAP (2)
  - CA 549

- **TESTICULAR**
  - Calcitonin (1)
  - hCG (1)
  - AFP

- **THYROID**
  - Calcitonin (1, 3)

- **BREAST**
  - CK-BB, CA 15–3 (1)
  - CA 549 (1, 4)

- **GASTROINTESTINAL**
  - CEA, CA 50, CA 19–5
  - CA 19–9, CA 72–4

- **PANCREATIC**
  - CEA (1), CA 50 (4), CA 19–9 (1, 2), CA 15–3

- **OVARIAN**
  - CK-BB, CA 125 (1), CA 15–3, CA 549, CA 72–4

- **COLORECTAL**
  - CEA (1, 3), CA 15–3
  - CA 19–9 (1), CA 50

- **BONE**
  - Alk. Phos.

1 = useful in monitoring
2 = useful in staging
3 = useful in making diagnosis
4 = useful in detecting the recurrence of cancer