Principles of Neoplasia

3

NEOPLASIA

I. BASIC PRINCIPLES

A. Neoplasia is new tissue growth that is unregulated, irreversible, and monoclonal; these features distinguish it from hyperplasia and repair.

B. Monoclonal means that the neoplastic cells are derived from a single mother cell.

C. Clonality can be determined by glucose-6-phosphate dehydrogenase (G6PD) enzyme isoforms.

1. Multiple isoforms (e.g., $G6PD_A$, $G6PD_B$, and $G6PD_C$) exist; only one isoform is inherited from each parent.
2. In females, one isoform is randomly inactivated in each cell by lyonization (G6PD is present on the X chromosome).
3. Normal ratio of active isoforms in cells of any tissue is 1:1 (e.g., 50% of cells have $G6PD_A$, and 50% of cells have $G6PD_B$).
4. 1:1 ratio is maintained in hyperplasia, which is polyclonal (cells are derived from multiple cells).
5. Only one isoform is present in neoplasia, which is monoclonal.
6. Clonality can also be determined by androgen receptor isoforms, which are also present on the X chromosome.

D. Clonality of B lymphocytes is determined by immunoglobulin (Ig) light chain phenotype.

1. Ig is comprised of heavy and light chains.
2. Each B cell expresses light chain that is either kappa or lambda.
3. Normal kappa to lambda light chain ratio is 3:1.
4. This ratio is maintained in hyperplasia, which is polyclonal.
5. Ratio increases to > 6:1 or is inverted (e.g., kappa to lambda ratio = 1:3) in lymphoma, which is monoclonal.

E. Neoplastic tumors are benign or malignant.

1. Benign tumors remain localized and do not metastasize.
2. Malignant tumors (cancer) invade locally and have the potential to metastasize.

F. Tumor nomenclature is based on lineage of differentiation (type of tissue produced) and whether the tumor is benign or malignant (Table 3.1).

Table 3.1: Examples of Tumor Nomenclature

LINEAGE OF DIFFERENTIATION	BENIGN	MALIGNANT (CANCER)
Epithelium	Adenoma	Adenocarcinoma
	Papilloma	Papillary carcinoma
Mesenchyme	Lipoma	Liposarcoma
Lymphocyte	(Does not exist)	Lymphoma/Leukemia
Melanocyte	Nevus (mole)	Melanoma

II. **EPIDEMIOLOGY**

A. Cancer is the 2nd leading cause of death in both adults and children.
   1. The leading causes of death in adults are (1) cardiovascular disease, (2) cancer, and (3) cerebrovascular disease.
   2. The leading causes of death in children are (1) accidents, (2) cancer, and (3) congenital defects.

B. The most common cancers by incidence in adults are (1) breast/prostate, (2) lung, and (3) colorectal.

C. The most common causes of cancer mortality in adults are (1) lung, (2) breast/prostate, and (3) colorectal.

III. **ROLE OF SCREENING**

A. Cancer begins as a single mutated cell.

B. Approximately 30 divisions occur before the earliest clinical symptoms arise.

C. Each division (doubling time) results in increased mutations.
   1. Cancers that do not produce symptoms until late in disease will have undergone additional divisions and, hence, additional mutations.
   2. Cancers that are detected late tend to have a poor prognosis.

D. Goal of screening is to catch dysplasia (precancerous change) before it becomes carcinoma or carcinoma before clinical symptoms arise.

E. Common screening methods include
   1. Pap smear—detects cervical dysplasia (CIN) before it becomes carcinoma
   2. Mammography—detects in situ breast cancer (e.g., DCIS) before it invades or invasive carcinoma before it becomes clinically palpable
   3. Prostate specific antigen (PSA) and digital rectal exam—detects prostate carcinoma before it spreads
   4. Hemoccult test (for occult blood in stool) and colonoscopy—detect colonic adenoma before it becomes colonic carcinoma or carcinoma before it spreads

CARCINOGENESIS

I. **BASIC PRINCIPLES**

A. Cancer formation is initiated by damage to DNA of stem cells. The damage overcomes DNA repair mechanisms, but is not lethal.
   1. Carcinogens are agents that damage DNA, increasing the risk for cancer. Important carcinogens include chemicals, oncogenic viruses, and radiation (Table 3.2).

B. DNA mutations eventually disrupt key regulatory systems, allowing for tumor promotion (growth) and progression (spread).
   1. Disrupted systems include proto-oncogenes, tumor suppressor genes, and regulators of apoptosis.

II. **ONCOGENES**

A. Proto-oncogenes are essential for cell growth and differentiation; mutations of proto-oncogenes form oncogenes that lead to unregulated cellular growth.

B. Categories of oncogenes include growth factors, growth factor receptors, signal transducers, nuclear regulators, and cell cycle regulators (Table 3.3).
   1. Growth factors induce cellular growth (e.g., *PDGFB* in astrocytoma).
   2. Growth factor receptors mediate signals from growth factors (e.g., *ERBB2* [*HER2/neu*] in breast cancer).
   3. Signal transducers relay receptor activation to the nucleus (e.g., ras).
      i. Ras is associated with growth factor receptors in an inactive GDP-bound state.

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