

## BIOLOGY OF NEOPLASMS

Reading: **Basic Pathology** Chapter 6, pp 165-178.

Summary: The characteristics of benign and malignant neoplasms are described.

I. DEFINITIONS. Abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissues and persists in the same excessive manner after cessation of the stimulus evoking the transformation; neoplasms serve no useful purpose and grow without respect for the needs of the host as a whole, usually growing at its expense, never to its benefit. Nomenclature: in general, for benign tumors use suffix -oma, for example, fibroma or adenoma for epithelial tumors of glandular origin; for malignant tumors of epidermal origin use prefix squamous cell carcinoma of, or adenocarcinoma of for tumors of glandular tissue - examples: adenocarcinoma of the stomach or squamous cell carcinoma of the cervix; for sarcomas, use suffix -sarcoma with tissue involved, for example fibrosarcoma; for leukemias/lymphomas use cell type involved, for example, lymphocytic leukemia.

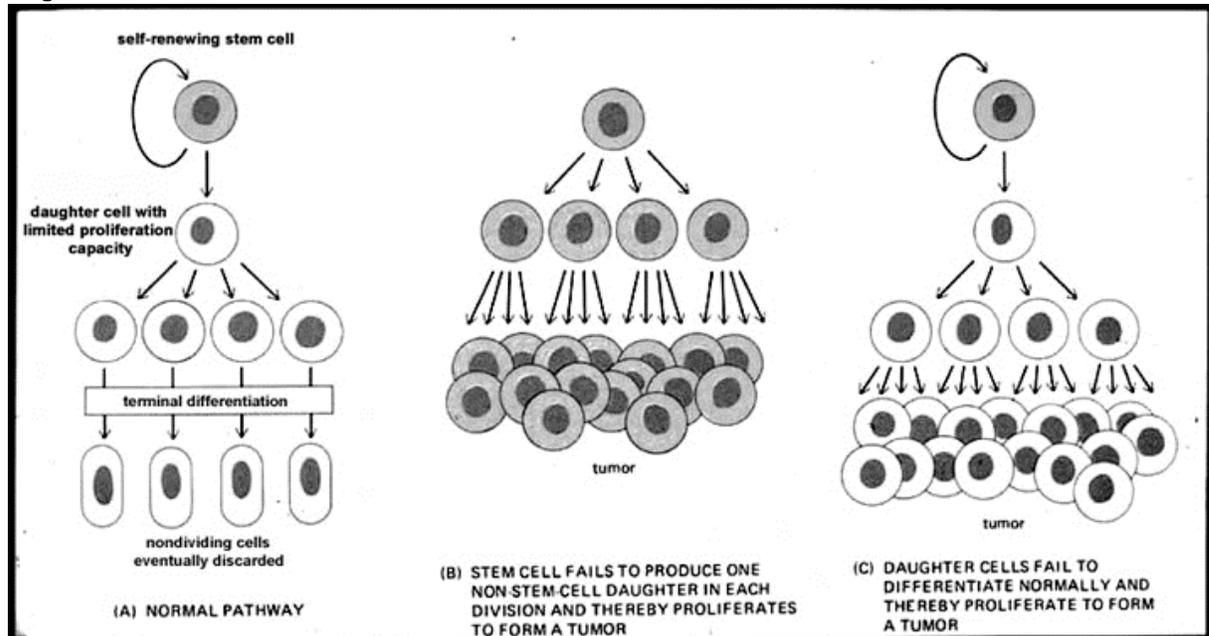
### II CHARACTERISTICS OF NEOPLASIA.

- A. Hyperplasia/metaplasia vs neoplasia: hyperplasia and metaplasia are responses to a specific stimulus. Hyperplastic and metaplastic tissues regress after the stimulus is removed. They are typical of the adult tissue and are well organized in structure. Neoplastic change is usually due to an unknown cause, the neoplastic changes tend to persist, they tend also to be disorganized, and atypical of the tissue of origin.
- B. Benign tumors have a well differentiated structure, grow slowly, and have few mitoses; they may expand, but often have a true capsule. They are non-invasive. Their growth may halt. They never metastasize, but they still may be dangerous. Contact inhibition of growth.
- C. Malignant tumors - have an atypical structure; infinite capacity to grow vs limited life of diploid cells; lose contact inhibition of growth and motion; frequently grow rapidly with many mitoses. They have no true capsule, tend to infiltrate surrounding tissues. They rarely stop growing. They tend to form metastases. They are often transplantable to tissue culture or animals ("nude mouse" test).

#### 1. Morphology

- a. differentiation - extent to which cells resemble normal adult cells from which neoplasm is derived; this includes both morphological and functional characteristics. Cancers arise from stem cells. Differentiated cancers, from maturation of undifferentiated cells; undifferentiated cancers, from proliferation without maturation (Figure 1). Embryonal tumors. Histologic grading of malignant tumors on the basis of their degree of differentiation.
- b. anaplasia - a measure of the lack of differentiation; the more anaplastic the less differentiated and the less like the normal adult tissue of origin; increasing anaplasia usually means increased growth rate.

Figure 1



- c. dysplasia - alteration in size, shape, or organization of adult tissue; a premalignant state; if full thickness of tissue is involved, it is a carcinoma-in-situ, a malignant tumor at its site of origin with its basement membrane intact. Human papillomatosis virus (HPV) and cervical cancer. Barrett's esophagus
  - d. pleomorphism, anisocytosis- variation in size and shape of cells; increased anaplasia usually means increased pleomorphism.
  - e. The connective tissue stroma including the blood supply of malignant tumors is usually normal. Tumor vasculature is a possible site of attack on cancers.
2. Growth, chromosome number: neoplastic cells do not usually grow faster than normal cells; however, they fail to stop growing.
    - a. benign tumors usually grow slowly and therefore have few mitoses; they may expand, but they often have a capsule that encloses the growth; their growth may halt.
    - b. growth rate depends on fraction of cancer cells growing; therefore, cancers have many mitoses; Frequently these are abnormal: abnormal mitoses cause changes in karyotype; aneuploidy - more or less than 46 chromosomes; some neoplasms associated with characteristic chromosomal defects such as deletions or translocations.
      - i. hyperchromatism - dark staining nuclei with abundant, active DNA; nuclei are polymorphic and large with respect to the cell size; large nucleoli. This is one basis for the cytologic diagnosis of cancer - use of flow cytometry to characterize cancers.
      - ii. malignant tumors rarely stop growing, but in some cases growth is associated with hormonal activity -

- breast and prostate.
    - iii. malignant tumors are infiltrative - they have no true capsule;
    - iv. increased anaplasia often means increased invasiveness.
- 3. Metastases - spread to a distant site; never seen with benign tumors, but characteristic of malignancy.
  - a. mechanisms of metastatic spread:
    - i. direct seeding of body fluids, cavities, and surfaces.
    - ii. lymphatic spread. Spread follows routes of drainage; especially important in carcinomas.
    - iii. hematogenous spread; especially seen in sarcomas.
  - b. Seed and soil hypothesis of metastasis; sites of metastases determined by:
    - i. The soil - presence in tissues of appropriate growth & chemotactic factors plus adhesion molecules. Tumor cells produce an angiogenic factor, VEGF-C that promotes their lymphatic spread.
    - ii. The seed - ability to lyse matrix due to matrix metalloproteinases (MMPs) and to acquire or lose various cell surface proteins. MMPs are produced by both cancer and surrounding stromal cells. MMP inhibitors are natural inhibitors of MMPs that may serve as future tumor inhibitory agents. Primary tumors contain many cell types, but metastases are most often monoclonal. Example: in breast cancers, tumor cells express CXC cytokine receptor 4, CXCR4, on their surface. Tumor cells detach from the primary, migrate in the lymphatic or vascular system, and arrest in organs with significant levels of the CXCR4 ligand, CXCL12, such as the lung, liver, or bone, sites of frequent breast cancer metastases.
  - c. Increasing anaplasia often associated with increased metastatic spread.
  - d. Staging of cancers based on size of primary tumor (T), local lymph node spread (N), and distant metastases (M)- TMN. Relationship between stage of tumor and prognosis.
- 4. Dangerous aspects of tumors
  - a. benign
    - i. positional - brain tumors
    - ii. necrosis, hemorrhage
    - iii. excessive production of a product such as a hormone.
  - b. malignant
    - i. progressive growth and metastasis
    - ii. infection
    - iii. cachexia. Role of TNF and IL-1
    - iv. production of various products such as hormones, enzymes, or oncofetal antigens such as CEA and  $\alpha$ -fetoprotein. Such products are often useful in diagnosis or following progress of tumors. Paraneoplastic syndromes are due to such anomalous products of tumor cells giving rise to symptoms not caused by local tumor growth or metastases.

5. Characteristics of malignant cells.
- a. Tumor progression (Figure 2).  
Cancers to be successful must lose sensitivity to growth inhibitory signals, resist apoptosis, avoid telomerase restrictions placed on growth, sustain angiogenesis, develop invasive and metastatic potential circumventing the immune system. Transformation is rare in human cells in the absence of alterations in the DNA repair (caretaker) system. Example of hereditary breast cancers.

Figure 2.

