

Cancer and the Immune System

Cells normally responsive to regulatory signals (growth factors, hormones, etc...)

- Cancer cells lose ability to respond to certain regulatory signals (why?)
 - receptors
 - signal transduction processes
 - gene mutation
 - viral nucleic acid insertion (oncogenes)
- Cancer-- loss of growth regulation

Terminology

Neoplasm-- "new growth", usually from a single cell (clonal expansion)

- **Benign**- does not invade healthy surrounding tissue, not capable of indefinite growth
- **malignant**- invasive into healthy tissue
- **metastasis**- spread of cancerous tissue
- Defined by tissue of origin
 - **Carcinoma**- arise from endodermal or ectodermal tissues (skin, glands)
 - **Sarcoma**- arise from mesodermal cells (bone, fat, cartilage)
 - **Leukemia/lymphoma**- arise from hematopoietic cells

Transformation

Transformation- alteration of morphology, growth properties

- caused by chemical carcinogens
- irradiation
- viruses (oncoviruses, retroviruses, DNA viruses)
- Properties of Transformed cells
 - decreased requirements for growth factors (serum)
 - no longer anchorage dependent
 - loss of contact inhibition
 - immortal
- Two phases-- initiation and promotion

Oncogenes

(1971) Proto-oncogenes vs Oncogenes

- high homology
- genes that control production of growth factors
- loss of regulation of growth factors due to slight mutation in single AA
 - induction of cell proliferation (growth factor [*sis*], growth factor receptor [*erbB*], signal transducers [*src, ras*], transcription factors [*jun, fos, myc*])
 - inhibition of cell proliferation [*p53*]
 - regulation of programmed cell death (*bcl-2* is a suppressor of apoptosis)

Induction of Cancer: Multistep

Multistep process of clonal expansion due to a series of somatic mutations that progressively convert the cell from normal to cancer

- Colon cancer begins as small, benign tumors in the colorectal epithelium (adenomas). These are precancerous, and as they grow they become more disorganized. Changes associated with specific sequence of gene changes, involving inactivation or loss of 3 anti-oncogenes (APC, DCC and p53)

Tumor Specific Antigens

Tumor specific transplantation antigens (TSTAs)-- unique to tumor cells and do not occur on normal cells. Result from mutations in tumor cells that generate altered proteins (present with MHC class I). Chemical or physical carcinogens and some virally induced tumors.

- **Tumor associated transplantation antigens (TATAs)**-- proteins that are not unique to tumor cells (may be fetal proteins that are not normally expressed in adults but would not be recognized as foreign)

Characterization of TSTAs

- Peptides bound to class I MHC on membrane of tumor cells are eluted with acid and purified by HPLC

OR

- cDNA libraries made from tumor cells and these are transfected into COS cells (monkey kidney transfected with SV-40 Lg T antigen). The plasmid containing the tumor antigen is replicated to high levels

TSTAs

Methylcholanthrene and UV light are two carcinogens used to generate tumor cell lines

- **When syngeneic animals are injected with killed cells from a carcinogen-induced tumor cell line they develop a specific immunologic response that can protect them against later challenge with live cells**
 - even when the same carcinogen induces two different tumors in different sites the TSTAs are different and do not protect against each other.
- **Virally induced tumors**
 - **express tumors antigens shared by all tumors induced by same virus**

TATAs

Majority of tumor antigens are not unique to tumors but are also present on normal cells

- may be proteins expressed only on fetal cells
- may be proteins expressed at low levels in normal cells but much higher levels in cancer (growth factors, growth factor receptors, oncogene products) such as EGF receptor, transferrin growth factor p97 (aids in transport of iron). 8000 on normal up to 500,000 on tumor cells

Oncofetal Tumor Antigens

Ags appear early in embryonic development before immune system acquires immunocompetence

- alpha-fetoprotein (AFP)-- found in the majority of liver
- carcinoembryonic antigen (CEA)
 - 90% of patients with advanced colorectal cancer have increased levels of CEA
- Not used to screen for tumor (since have basal levels) but can be used to monitor treatment and growth of tumors