LECTURE 40
CANCER: Microevolution of bad citizen cells

Chapt. 23, p. 1313-1326; Figs. 23–1 to 23-15.

Cancer as a microevolutionary process

- a healthy body functions like balanced ecosystem; cells respond to whole-body homeostatic control mechanisms & collaborate for good of the whole.
- "selfish" cells jeopardize chances of reproductive success for the organism
- somatic cells all die; cooperate so germ cells have shot at immortality
- in cancer, a 'selfish" cell fails to respect normal cell proliferation controls, circumvents mechanisms designed to eliminate it, generates clone of "bad citizen" cells (birth of a tumor).
- cancer cells undergo own "microevolution" in terms of competition for resources, survival & reproduction (except: evolutionary dead end!)

Cancer cells defined by two heritable properties:

1. reproduce without restraint
2. colonize foreign tissue

Fig. 23-3: Benign vs malignant tumors

- **benign neoplasm:** group of cells that proliferate in defiance of normal controls but can't metastasize to other tissues & generate 2° tumors
- **malignant tumor cells:** proliferate relentlessly AND are invasive/**metastatic**
- **classification of malignant tumors via cell type origin:**
  - CARCINOMAS: arising fr. epithelial cells; 90% of human tumors (why?)
    - **adenocarcinoma:** arising from glandular epithelia
    - **prostate gland carcinoma:** if not eradiated early, preferentially metastasizes to bone marrow sites: **Fig. 23-1**
    - **basal cell carcinoma:** arising from **keratinocyte stem cell;** locally invasive/surgically accessible; rarely metastatic
    - **melanoma:** arising from melanocyte lineage; prone to rapid metastasis; often fatal after metastasis
  - SARCOMAS: arising from connective tissue or muscle cells
    - eg., osteosarcoma (arising from bone cell lineage)
  - LEUKEMIAS: arising from hemopoietic cells
  - OTHER: various neurological tumors
- **Classification of benign vs malignant tumors (2 examples)**
  - adenoma: benign glandular epithelial tumor (vs. adenocarcinoma)
  - chondroma: benign cartilage tumor (vs. chondrosarcoma)
- **Most cancers derive from single abnormal cell w/ somatic mutation(s)**
  - metastases trace to single primary tumor, presumed derived from single abnormal cell; defect is heritable/genetic
  - at detection, typical tumor is>10^9 cells, often includes some normal cells
  - evidence for clonal origin of abnormal cells in tumor:
    - **Philadelphia chromosome**: specific chrom. transloc'n seen in all leukemic white blood cells in **chronic myelogenous leukemia** patients (not seen in their non-tumor cells)
    - **In females,** tumor cells all have SAME X chrom. inactiv'd (female tissues are mosaic w/ regard to whether paternal or maternal X-chrom is inactive; X-inactiv'n occurs during embryogenesis; is random)
  - **Evidence for somatic mutations in tumor cells:**
    - Philadelphia chrom. (see above).
    - many **carcinogens (cancer causing agents)** are **mutagenic**
      1. *chemical carcinogens:* cause nucleotide seq changes
      1. *ionizing radiation:* chrom. breaks, transloc'ns
      1. *viruses:* introduce foreign DNA into host cell

    - many examples of mutations or "loss-of-heterozygosity" for specific genes in tumor cells relative to non-tumor cells in adjac. tissues (some exs. here; more in later lectures)
    - individuals w/ **mut'ns in DNA repair enzymes** are highly susceptible to various cancers (e.g. **xeroderma pigmentosum**: high rate of skin cancer due to mut'ns in repair enzymes for UV-damaged DNA)
- **Single mutation not sufficient to cause cancer**
  - studies of cultured somatic cells: ~10^{-6} spontaneous mutations/gene/cell division (finite limits to DNA replic'n/repair); given ~10^{16} cell divisions in human lifetime, each gene undergoes ~10^{10} mut'ns in a lifetime!
  - **Fig. 23-7:** incidence of most cancers increases w/ age; mult. rare mut'ns must accumulate in same somatic cell lineage
  - Mouse models: many genes mutated in human cancers have been studied in mice; mut'ns in single genes typically insuffic't to cause cancer; cells must accumulate addit'nal mut'ns to be tumorigenic
- **Cancers "evolve" slowly, in stages, beginning w/ mildly abnormal cells**
  - **Fig. 23-8: Time lag** betw/ mutagen exposure & tumor form'n is YEARS
    - probably true for all cancers
  - Chronic myelogen. leukemia begins slowly w/ increased nrs of wbc; yrs pass before changing to rapidly progressive, terminal illness ; in late phase, abnorm. wbc w/ mult. chr. defects outnr. wbc w/ just Ph. chrom.)
  - **Cervical cancer:** cancer of epithelial cells at opening (cervix) of uterus
    - **Normal cervical epithelia:** stratified, prolifer'n in basal layer only; diff'd cells above (resembles epidermis)
    - **Fig. 23-9: Stages of progress'n in cerv. carcin. (as seen in sections)**
      1. **Low grade intraepithelial neoplasia (i.n.)**: 1st step; mitosis in lower 1/3 of epith; less diff'n in upper strata
      2. **High grade i.n.:** mitosis in all layers; no diff'd cells; many abnormally large cells & nuclei; condit'n may persist or regress; but 30-40% progress to i.c. over period of a few yrs
      3. **Invasive carcinoma:** malignant cells "eat" thru basal lamina
    - **Fig. 23-10:** stages as seen in **Pap smear** of cerv. epith.
- **Tumor progression involves successive rounds of mutation & selection**
  - **Fig. 23-11: tumor clonal evolut'n,** like evol'n in any popul'n depends on:
    - mutation rate (high mut. rate/genetic instability speeds tumor evol'n)
    - number individuals (target pool for add'l "hits"/mut'ns)
    - rate or reproduct'n (mitosis) (mut'ns increasing cell division rate: larger tumor/greater chance of add'l "hits" to speed tumor evol'n)
    - selective advantage for indiv (cell) w/ new mut'n (if it <u>increases</u> 1st 3)
- **Most cancer cells are genetically unstable**
  - **Fig. 23-12:** abnormal chromosomes in breast cancer cell; suggests DNA repair grossly defective in these cells; mutational "flood gates" open
  - **Fig. 23-13: Genetic instability & tumor progression**
- **Cancer depends on loss of controls limiting cell proliferation**
  - **Fig. 23-14:** Normal & deranged control of cell production via stem cells
    - Mut'ns allowing cells to ignore commitmt or diff'n signals
    - Mut'ns allowing cells to ignore **replicative senescence** or PCD signals
  - **Fig. 23-15: Steps in process of metastasis**
    - express proteases to digest basal lamina & endothelium of bv
    - enter blood stream
    - adhere to bv wall in new tissue & extravasate into tissue
    - proliferate in new tissue

6 Key Properties of cells capable of cancerous growth: what are they?