

LECTURE 44 CANCER THERAPIES

Chapt. 23, p. 1353-61; Figs. 4-10 & -15; Figs. 23-5, -40 thru -45

Finish section on colorectal cancer:

Karyotype analysis reveals gross chromosomal abnormalities in some cancers (e.g. Ph chrom. in leukemic cells of CML patients)

- **karyotype**: complete set of metaphase chromosomes of a representative mitotic cell (homolog. chrs. in pairs & arranged by size)
- **chromosome painting: Fig. 4-10** (karyotype in color)

Fig. 23-40: Two different types of genetic instability in colorectal cancers as seen by karyotype analysis

- Most colon cancers: multiple, gross abnormalities in chrom. nr. & structure due to translocations, breakage-fusion cycles, etc
- Others show few gross chrom abnormalities; mainly **point mutations or small deletions/insertions** in DNA sequence
 - **Example: hereditary nonpolyposis colorectal cancer**
 - distinct from FAP (Lect. 42)
 - not associated with increased nr. polyps/adenomas
 - individuals at risk are heterozygous (+/-) for mutations in genes encoding **DNA mismatch repair enzymes**
 - spontaneous mut'ns disabling remaining good copy causes cell & its descendants to have 100X higher spont. mut'n rate

Fig. 23-41: Steps in colorectal tumor progress'n correlated w/ specific mut'ns

- more than one route to c. cancer
- but most typically
 - APC inactiv'n probably early (already in benign polyps); increases prolif'n w/out much disturbing cell diff'n
 - Later, K-Ras activating mut'ns (in large but not small polyps); disturb diff'n & tissue histology (in culture, these cells are "transformed"/pile up)
 - Later still, P53 & other tumor suppressors: loss is rare in polyps, common in malignant c. carcinoma cells

Fig. 23-42: Each case of cancer characterized by own set of genetic lesions

CANCER TREATMENT

Prevention

- Studies suggest risk factors vary for each cancer, non-genetic factors often include smoking (strong assoc'n w/ MANY cancers), alcohol, lack of exercise/activity, obesity, exposure to certain chem.. & infect. agents
- for more info'; NOT on exam, see: <http://www.cancernet.nci.nih.gov>

Diagnosis & treatment:

- Screening, early detection (good medical care) stem mortality rates
- **Fig. 23-43:** Current "**cytotoxic**" therapies exploit loss of cell cycle control & genetic instability of cancer cells
 - E.g., **Radiation therapy**: cancer cells tend to be more sensitive to damaging effects of ionizing radiation due to failure to arrest & repair
 - OR may be *resistant* to it if they have mut'ns allowing them to avoid apoptosis signals!
- Most malignant, late stage tumor cells are heterogeneous due to gen, instab.; rapid microevol'n possible; resistance to therapies

- Example: **amplif'n of *Mdr1*** encoding ABC transporter; pumps certain lipophilic drugs out of cell; leads to **multidrug resistance** in tumor cells
- **Amplif'n of *dhfr* genes**, encoding DHFR enzyme targeted by chemotherapy agent **methotrexate**; amplified *dhfr* genes: double minutes or heterogeneously staining region (like Myc in **Fig. 23-28**)

New therapies may emerge from more knowledge of cancer biology (and cell biology generally!)

- New areas of progress in **breast cancer**:
 - **Tamoxifen**: estrogen antagonist; prevents or delays cancer recurrence
 - 25% of breast cancers show elevated Her2 (EGF receptor family member); therapy in trials: reducing Her2 using an **anti-Her2 antibody**
- **Cancer treatments designed to attack cells lacking p53**
 - In trials: kill tumor cells lacking p53 by injecting mutant adenovirus lacking p53-blocking protein (like E6 of papillomavirus) into tumor; virus **ONLY** replicates in/kills cells lacking p53
- **Treatments that choke tumor growth by targeting their blood supply**
 - Clinical trials with angiogenesis inhibitors
- **Designer drugs: small molecules designed to target specific oncoproteins**
 - Treatment for 95% of **chronic myelogenous leukemias (CML)**
 - **Fig. 23-44: Bcr/Abl oncoprotein** is a hyperactive tyrosine protein kinase; stimulates product'n of excess wbc
 - **Gleevec**: designer drug for CML from Novartis, blocks Bcr/Abl kinase activity by binding ATP pocket of kinase domain; v. successful for halting chronic phase of CML (less so for acute phase where gen. instb. has set in)

Understanding cancer biology in DETAIL will lead to rational, tailored treatments that target cancers more precisely