

## LECTURE 41 CARCINOGENS & TUMOR PROMOTION

Chapt. 23, p. 1326-1336; Table 23-1, Figs. 23-17 to 23-26.

### Preventable causes of cancer

- dev of cancer reqs many steps each affected by multiple genetic, environmental, diet & life style factors
- DNA replication is imperfect, so mutations can never be absolutely prevented
- however, popul'n studies suggest SOME contributing factors r AVOIDABLE
  - **Table 23-1:** incidences of diff't cancers vary in diff't countries; immigrants show incid. profile of new not old country, so lifestyle & diet clearly imp't
  - Mormons who don't smoke, drink alcohol or caffeinated drinks, get cancer at rates 1/2 that of general US popul'n

### Many cancer-causing agents damage DNA

- including chemical carcinogens, UV light, X-rays, viruses
- carcinogenic w/ repeated application on animal skin:
  - various aromatic hydrocarbons & derivatives, including nitrosamines

### Fig. 23-17: The Ames test for mutagenicity

- economical assay using Salmonella bacteria w/ revertable point mut'n in *his*
- tests effect of suspected carcinogen on mut'n rate in bacteria (*his* revertants)
- assumes carcinogen's effects on DNA in bact & human cells are similar
- modific'n: add liver enzymes to mix (rationale: mutagenic effect may be due to metabolites in bloodstream generated by "detox" processing in liver)
  - cytochrome P450 oxidases convert ingested toxins into excretable metabolites; some, unfortunately, mutagenic (e.g., metabolites of benzopyrene, in tobacco smoke & coal tar; & of aflatoxin, from mold)
  - **Fig. 23-18:** metabolic activation of a carcinogen
    - aflatoxin B<sub>1</sub> to aflatoxin-2-3-epoxide which reacts w/ guanine in DNA

### TUMOR PROMOTION: Development of cancer can be PROMOTED by factors that don't alter DNA

- genetic changes induced by mutagens are irreversible but may be phenotypically LATENT until further events (eg. prolifer'n & diff'n) uncover them
- the **mutagen/carcinogen is the "tumor initiator"** but other factors (tumor promoters) affect whether mutated cells proliferate & form tumors
- **tumor promoters:** not mutagenic, but increase freq of tumor formation in tissue previously exposed to mutagen/tumor initiator
  - eg. phorbol esters: artifical activators of PKC, activate part of phosphoinositide signaling pathway, stimulates cell prolifer'n
  - **Fig. 23-19:** Some possible schedules of exposure to tumor initiator and tumor promoter, and their outcome
  - **Fig. 23-20:** Effect of tumor promoter: uncover effects of carcinogens even after long delay (ex. Papillomas: after carcin. exp., some stem cells are mutated, but defects only evident when tumor promoter stimulates prolifer'n - then large clones of mutant progeny cells form, and serve as pool for next "hit"/tumor evolution)

### Viruses & other infect'ns contrib. to signif. proport'n. of cancers

**Table 23-2: Viruses associated w/ human cancers** include papillomavirus (cervical c.), hepatitis-B (liver c.), Herpes virus & HIV (Kaposi's sarcoma), etc.

- viruses must act in conjunc'n w/ other factors since
  1. #infected >> #w/ tumors
  2. delay of many yrs betw/infection & cancer

- many v. act indirectly (eg. HIV causes immun. defic. that allows HSV to cause chronic rather than episodic infect'ns; HIV infect'n "promotes" HSV's carcinogenicity)

### Identification of carcinogens reveals ways to avoid cancer

**Fig. 23-22:** Age-adjusted cancer death rates, US 1930-1996.

- Tobacco smoke is most signific. environmental cause of cancer
- Unexpected findings: our own HORMONES are significant factors in cancer!
  - **Fig. 23-23:** Effects of childbearing on risk of breast cancer
- Other epidemiological studies on cancer & risk factors:
  - **Fig. 23-8:** Delayed onset of bladder cancer in workers exposed to carcinogen 2-naphthylamine

**Identifying environmental factors contributing to cancer & assessing risks involved is difficult:** for ex. agricultural fungicides are mildly carcinogenic at high doses in lab animals, but, w/out these, aflatoxin contam. of food would cause far more cancers!

### FINDING CANCER CRITICAL GENES

- The challenge: tumor cells have mult. mut'ns; some causally related to tumor evol'n, others just mutated by chance due to genetic instability.
- ~100 genes now clearly identif'd as cancer-critical (w/ mut'ns shown to be causally linked to cancer)
  - **Fig. 23-24: cancer critical genes fit into two broad categories:**
    - **oncogenes:** their mutant proteins (oncoproteins) are **overactive**; allow cells to proliferate when they should not; usually dominant mutations
    - **tumor suppressors:** normally, their protein products suppress cancer; their genes are **DELETED or INACTIVATED** in cancer cells; usually recessive mutations

**Different methods are used to identify gain-of-function (oncogenes) vs loss-of-function (tumor suppressor) mutations in tumor cells**

- **Oncogenes:** many 1<sup>st</sup> identif'd as
  - genes fortuitously "highjacked" by retroviruses subsequently rendered oncogenic (causing tumors in infected animals); show dominant transforming activity in cultured cells (**Fig. 23-25**) (e.g., point mut'ns that hyperactivate Ras, found in many cancers)
  - gene interrupted/alterd at chrom. translocation break points
  - **Fig. 23-27: Three ways to convert proto-oncogene to oncogene**
    - hyperactive protein (eg. mutant Ras, trunc'd EGFR in glioblastomas)
    - elevate protein by gene amplific'n (e.g., *myc*, **Fig. 23-28**)
    - chromosomal rearrangement that hyperactivates expr'n of gene (eg. *Myc* in Burkitt's lymphoma)
- **Tumor suppressors:** more difficult to identify
  - some identif'd in studies of rare hereditary cancers (eg. retinoblastoma)
  - **Fig. 23-26: The genetics of retinoblastoma**
    - Rare (1/20,000) childhood tumors due to somatic Rb mut'ns in retinal precursor cells (loss of Rb: no brakes on cell division cycle)
    - Freq deletion of band on chrom 3 suggested location of gene (Rb)
    - Hereditary & non-hereditary forms (+/- and +/+ individuals, resp.)
    - Rb also lost in some later onset, adult cancers: lung, breast, bladder
  - scanning chroms & genome for "loss of heterozygosity" (loss of remaining good copy of gene) in tumor vs adjac. normal tissue (**Fig. 23-29**)