

LECTURE 43 Tumor Progression & Metastasis

Chapt. 23, p. 1346-53; Figs. 23-34, -35, -37 to -39; Table 23-3

P53^{-/-} cells fail to pause to repair DNA damage; vast increase in genetic instability:

- **Fig. 23-3:** How replic'n of damaged DNA leads to chromosome abnormalities
 - Accidental break in chrom. DNA in P53^{-/-} cell leads to escalating damage after each round of replication (**breakage-fusion cycle**)
 - Contributes to gene amplific'n mechanisms/tumor evolution

DNA tumor viruses activate cell's replication machinery by blocking action of key tumor suppressor genes

- **Fig. 23-34:** How certain papillomaviruses are believed to give rise to cancer of uterine cervix
 - Viral chrom. is stably maintained in basal cells as circular ds DNA in wart/benign infection; replicates when host DNA does
 - Rare integration of part of viral chrom. into host chrom. can ectopically activate viral genes whose prot. products interfere w/ cell prolifer'n control
- **Fig. 23-35: Activation of cell prolifer'n by a DNA tumor virus:**
 - Papillomavirus E6 & E7 proteins sequester host p53 & Rb respectively
 - E6 binding leads to ubiquitylation & proteolysis of p53
 - allows cell to prolifer & accumulate more abnormalities

Telomere shortening may pave way to human cancers

- In mouse, sarcomas & leukemias are major cancers
- In humans, carcinomas prevail
- Therapies based on mouse studies often fail in human cancers
- Mice have longer telomeres (repetitive DNA at ends of chroms, maintained by telomerase) that don't tend to shorten w/ age
- Human chroms. suffer gradual loss of telomeres over long lifespan & during **replicative cell senescence**
- Mice w/ mutant telomerase show increased incidence of cancer in old age
- **Fig. 23-36: how shortened telomeres may lead to chrom. abnormalities**
 - Most human cells lack telomerase; telomeres shrink after many divisions.
 - If p53 lost, no replic. Senescence; breakage fusion-cycle ensues (23-33)
 - Some mut. cells may survive by reactiv'g telomerase, restoring suffic. genetic stability; tumor progression may occur

Overcoming barriers to metastasis during tumor progression: Fig. 23-37

- Fig. 19-24: Loss of E-cadherin (homophilic adhesion molecule)
- Increased cell motility freq seen in metastatic cells

Fig. 23-38: Colorectal cancers evolve slowly via succession of visible changes

- Carcinoma of epithelial lining rectum and colon
- (60,000 deaths/yr in US; ~11% of total cancer deaths/yr)
- diagnosis typically late in life (90% after age 55)
- progression follows fairly typical, slow course (10-35 yrs to cancerous stage)
- early diagnosis & surgery removing early **adenomatous polyps (23-38A)** reduces mortality significantly
- carcinoma stage (23-38B): larger polyps that invade underlying muscle layer

- **Fig. 23-39:** colon epithelia of patient w/ **familial (hereditary) adenomatous polyposis coli (FAP)** (section in 38A) covered w/ small polyps (normal colon epith. smooth w/ undulations); progr'n to cancer in ~12 yr. in FAP patients
- **Table 23-3:** A few key mutations common to majority of colon cancer cases
 - Mutations in **K-ras, p53 & APC** are most common
 - APC lost/inactivated in ALL FAP patients
 - In non-FAP, 60% of patients have lost APC in tumor cells but not elsewhere (like Rb in non-hereditary retinoblastoma tumors)
 - APC inhibits Wnt signaling by binding b-catenin, preventing its entry into nucleus (in absence of APC, b-cat. is cofactor for activ'n of genes stimulating prolif'n of colonic epith.
 - SMAD4 lost/inactivated in 30% of cases (mediates TGFbeta signaling)