

LECTURE 42

CANCER CRITICAL GENES: Ras, Rb, p53 & more

Chapt. 23, p. 1337-1345; Fig. 8-70, Figs. 23-27 to -33.

From Lecture 41 notes: cover Figs. 23-27, -28, -29
MOLECULAR BASIS OF CANCER CELL BEHAVIOR

- **Identif'n of cancer critical genes:**
 - heyday 1970's - 90's; what are normal functions of these genes?
 - progress in cell & dev biol, genomics/bioinformatics, & transgenic mouse techniques has converged to help define regulatory pathways where these genes normally function & how they go awry in cancer (still much to learn!)
- **Cancer critical (cc) genes essentially components of cell prolifer'n machinery & cell communic'n signaling pathways imp't in normal tissue dev & morphogenesis** (incl. Wnt, Hh, TGF β , Notch, RTK's)
 - some cc gene products affect cell's response to extracellular signals
 - others affect cell's internal program (cell cycle, apoptosis, etc)
 - others affect cell's ability to interact w/ neighboring cells
 - **Fig. 23-31:** the pathways intersect/are integrated in complex ways
- **Transgenic mice** espec. useful in studying synergy betw/ cc genes in vivo; testing models of tumor progression
 - **Fig. 8-70:** Making transgenic mice. Regulatory region (transcr. enhancer elemts) included in transgene determine what tissues express it
 - **Fig. 23-30:** Collaboration of oncogenes in transgenic mice
 - Myc & Ras oncogenes stimulate cell growth & c. cycle progression
 - neither oncogene alone is sufficient to cause tumors at high freq altho' some "neoplastic" tissue growth occurs; rare, late onset tumors suggest additional mut'ns must accumulate
 - mating Myc mice x Ras mice: progeny with both oncogenes show higher freq & earlier onset of tumors; fewer addit'l mut'ns req'd
- **Many cc genes regulate cell proliferation/cell cycle**
 - mutant Ras or trunc'd EGFR: stimulate cell prolifer'n; GFs no longer limiting
 - **Fig. 23-32: Rb (tumor suppressor)** normally limits cell cycle progression via pathway for G₁- checkpt.
 - mut'ns in this pathway that remove "brakes" on cell cycle:
 - loss of Rb or p16
 - over-activity of CDK4 or cyclinD1
- **Mut'ns in genes regulating apoptosis allow cancer cells to escape suicide**
 - in many tissues, cell prolifer'n balanced by loss of excess cells by apoptosis
 - apoptosis also has vital role in removing abnormal or damaged cells
 - malignant cells must circumvent apoptotic signals
 - B-cell lymphoma: transloc'n causes over-express'n of **Bcl2**; Bcl2 blocks apoptosis
 - **p53: prob. most imp't tumor suppressor**; mut'd in 1/2 of all cancers
 - inducible in response to UV, DNA damage, low O₂, other stresses
 - regulates DNA damage response, other stress responses: triggers apoptosis of damaged cells OR arrests c. cycle until DNA repaired
 - p53-/- cells escape apoptosis; don't arrest to repair damaged DNA; resulting genome corruption & genetic instability opens mut'n floodgates; speeds microevol'n of tumor cells
 - p53-/- mice develop cancer by 3 months of age
- **Fig. 23-33:** chromosomal abnormalities, gene amplific'n, & gene loss due to replic'n of damaged DNA

