BREAST CANCER 2
tumor-suppressor genes
proto-oncogenes

READING: pp. 202-220

THE CELL CYCLE

Mitosis (M-phase)

Checkpoints
proto-oncogenes (+)
tumor suppressors (-)

INHERITED BREAST CANCERS BRCA1, BRCA2

“Each year in the United States nearly 200,000 women are diagnosed with breast cancer. For as many as 20,000 of these women, the diagnosis comes not as a shock but as the grim conclusion to a dreadful wait. They are women with a strong family history of breast cancer, perhaps with grandmothers and mothers and sisters who fell victim to the disease while still in their thirties and forties.

These are women who harbor a gene that almost guarantees them a place on an appalling statistical list...”

BRCA 1 mapped genetically Mary Claire King (1994, UC Berkeley)
BRCA 1 cloned by positional cloning Gailo Kamb, Mark Skolnick et al (1994)
**TUMOR SUPPRESSOR GENES**

**FUNCTION**

"STOP" signal at cell cycle checkpoint: DNA repair or apoptosis

**LOSS-OF-FUNCTION**

- no checkpoint stop; no DNA repair; cell cycle continuously cycles

**STOP**

- Inherited BRCA1 mutation (breast cancer frequency): 20% by age 40y, 50% by age 50y, 85% by age 60y
- Inherited germline mutation
- Inherited somatic mutation
- "TWO-HIT MODEL"

**CANCER GENES**

Accumulation of multiple mutations

Potential cancer genes - about 100 genes

1. Inappropriate signals about need for cell division (hormonal signaling pathways: growth factors)
2. Malfunctions in CDK-cyclin complexes controlling cell cycle transitions
3. Checkpoint breakdowns leading to DNA instability
4. Loss of programmed cell death (cell suicide)

**G₁-to-S TRANSITION**

- CDK2
- CDK4
- cyclinA
- cyclinD
- cyclinE
- Rb (retinoblastoma; E2F inhibitor)
- E2F (transcription factor)
- p21
- p53
- BRCA1
- BRCA2

Some proteins ALL ARE responsible for CANCER progression through GENES transition and checkpoint.

CDK enzymes: are cyclin-dependent protein kinases, control the activity of other proteins by phosphorylating them

Cyclins: are proteins necessary for CDK activity
**PROTO-ONCOGENE**

HORMONAL REGULATION

\[ \text{MUTATION} \rightarrow \text{NOT REGULATED} \quad \text{(on/off)} \]

\[ \text{PROTO-ONCOGENE} \rightarrow \text{ONCOGENE} \]

(NORMAL GENE PRODUCT) \rightarrow (MUTANT GENE PRODUCT)

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**DOMINANT ONCOGENE**

("GAIN-OF-FUNCTION" MUTATION)

\[ \text{mutant gene} \rightarrow \text{excessive protein or abnormally active protein} \quad \text{("always go")} \]

\[ \text{normal gene} \rightarrow \text{on/off} \]

ONE MUTANT COPY AND IT IS A GO = DOMINANT

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**MUTATIONS ACTIVATING ONCOGENES**

**THREE ACTIVATION TYPES**

**PROTEIN STRUCTURE CHANGED**

a) increased enzyme activity
b) loss of regulation

c) increased expression (through misregulation)
d) increased protein stability, prolonging its existence

e) gene duplication

**CHROMOSOMAL TRANSLOCATION**

a) expression in wrong cell type or at wrong time
b) constitutively active hybrid protein

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**ONCOGENE: RAS**

HORMONE: BREAST CANCER: Her2/EGF

HORMONE + RECEPTOR

SIGNAL TRANSDUCTION CASCADE

\[ \text{G-PROTEIN-RAS} \rightarrow \text{ONCOGENE} \rightarrow \text{growth} \]

transcription factor stimulates growth

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**HUMAN PAPPILOMA VIRUS (HPV)**

GENITAL WARTS

CERVICAL CANCER

AGE 14 to 19y (female) 25% HPV prevalence
AGE 20 to 24y (female) 45% HPV prevalence

14,000 U.S. women/year diagnosed cervical cancer
3,900 U.S. women/year die
"HIGH RISK" HPV TYPES

HPV - Family of about 100 DNA-based viruses

**GENITAL WARTS**
- Types 6 and 11 (90% of all cases)

**CERVICAL CANCER**
- Types 16, 18, 31 and 45

HPV-induced cancers often have viral sequences integrated into the cellular DNA.

E6 inhibits p53
E7 inhibits p53, p21, and RB.

A group of about 30-40 HPVs typically transmitted through sexual contact.

Some of the HPV "early" genes, such as E6 and E7, known to act as ONCOGENES that promote tumor growth and malignant transformation.

TEXAS LAWMAKERS REJECT HPV VACCINE ORDER

Texas lawmakers rejected Governor Rick Perry’s HPV vaccine order last week. The bill essentially would bar state officials from requiring the vaccine for four years. The Governor still has the opportunity to veto the bill.

Republican Rep. Dennis Bonnen, the bill’s House sponsor, said he believes it is fair and reasonable. “I think the governor should see this as the Legislature making a very clear and respectful statement, and I hope he’ll accept our wishes,” Bonnen said.

Governor’s spokeswoman, Krista Moody, had this to say on his behalf: “The governor looks forward to a day when cervical cancer is eradicated and Texas women no longer have to cope with the devastating effects of this disease,” she said, adding that the Legislature’s actions will “delay that day for another four years.”

Harris’ Gardasil, the vaccine protects against four strains of the sexually transmitted HPV infection. The U.S. Food and Drug Administration recently approved the vaccine for girls and women ages 9 to 26.

Published May 31st, 2007 in HPV Vaccine: A blue chip_tool. Protects against four HPV types, which together cause 70% of cervical cancers and 90% of genital warts.