SOMATIC MUTATIONS, GERM-LINE MUTATIONS, AND BREAST CANCER

READING: pp. 202-220

CANCER overview
- Class of diseases
- Uncontrolled cell division
- Spread to adjacent tissues
- Metastasis: cancer cells spread by bloodstream or lymphatic system

BREAST CANCER
- Cancer cells spread by bloodstream or lymphatic system

NEW CASES OF CANCER

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of new cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>800,000</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>203,500</td>
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<tr>
<td>Prostate</td>
<td>189,000</td>
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<tr>
<td>Lung</td>
<td>169,400</td>
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<tr>
<td>Colon-rectum</td>
<td>148,300</td>
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<tr>
<td>Urinary system</td>
<td>90,000</td>
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<tr>
<td>Uterus</td>
<td>52,300</td>
</tr>
<tr>
<td>Pancreas</td>
<td>30,300</td>
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<tr>
<td>Ovary</td>
<td>23,300</td>
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</tbody>
</table>

1 in 8 women expected to be diagnosed sometime during their lives

AGE CONSIDERATIONS
- 12 y - Early menstruation - risk factor (estrogen)
- 30 y - Late childbearing (1st child) - risk factor (estrogen)
- 35 y - Breast cancer uncommon below this age
- 40 y - Regular mammograms (yearly)
- 40 y - Many breast cancers estrogen-dependent (35%)
- 50 y - Most cancers occur over this age
- 55 y - Late menopause - risk factor (estrogen)
- 60 y - Risk for breast cancer especially high

Breast cancer occurs more often in white women than African American or Asian women

Breast cancer
(NIH website)

41,000 US women will die this year

SEPARATION OF SOMATIC CELL LINE AND GERM LINE

Mutations
- Chemical carcinogens (radiation, UV, X-ray)
- Environmental stress (germ-line mutations)
- Embryo proper (spontaneous, all tissues)
- Germline: female eggs, male sperm
- Somatic cells (precursors): all tissues

1/3 individuals will not survive from diagnosis

older adults: 1/4 all deaths due to cancer

BREAST CANCER (some demographics)

- Breast cancer occurs more often in white women than African American or Asian women

- 1/4 of all deaths due to cancer

- 1/3 of all deaths due to cancer
**DUCTAL CARCINOMA**
- most common type of breast cancer
- begins in the lining of the ducts

**LOBULAR CARCINOMA**
- begins in the lobules of the mammary glands

**TUMORS**
- abnormal growth of tissue

**BENIGN TUMORS**
- self-contained. Do not spread to other tissues. Not invasive.
- cause problems by increasing in size until they interfere with the function of neighboring organs.

**CANCEROUS TUMORS**
- single cell + clonal descendants.
- accumulation of multiple mutations in array of genes (4-7 somatic mutations minimum)

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**CELL PROLIFERATION**

Uncontrolled cell division comes from accumulation of genetic defects that lead to too much "go" signal, too little "stop" signal, and loss of cell suicide

**THE CELL CYCLE**

- Mitosis (M-phase)
- Checkpoints
- proto-oncogenes (+)
- tumor suppressors (−)

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**BREAST CANCER PROGRESSION**

- **Stage 0:** Pre-cancer cells in milk duct lining of breast
- **Stage I:** Spread to other breast cells
- **Stage II:** Spread out of breast to lymph node (under the arm)
- **Stage III:** Locally Advanced Cancer
- **Stage IV:** Metastatic Cancer

**Local treatment**
- Surgery
- Radiation therapy

**Systemic treatment**
- Chemotherapy
- Hormonal therapy

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**TIME LINE OF BREAST CANCER**

- suggests probable heterogeneity.
- primary breast cancers begin as single (or many) cells which have lost control regulation of differentiation and proliferation but remain confined within the basement membranes of the duct or lobule. as these cells go through several doublings, at some point they break through the basement membrane of the ductule or lobule and ultimately metastasize to distant organs.

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**NORMAL BREAST CELLS**

- cell division in response to hormonal signaling.

**MILK DUCTS**

- normal breast cells
- cell division in response to hormonal signaling.

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**MAMMARY GLANDS**

- normal breast cells
- cell division in response to hormonal signaling.
TANOUYE POSTDOC LINEAGE: SCAFE FAMILY

Bilateral breast cancer (30's)
Ovarian cancer (middle 50's)
Daria 41y 39y 34y

BRCA example

TUMOR SUPPRESSOR GENES

FUNCTION
"STOP" signal at cell cycle checkpoint; DNA repair or apoptosis

LOSS-OF-FUNCTION
inherited BRCA mutation; breast cancer frequency:
20% by age 40y, 50% by age 50y, 85% by age 60y
spontaneous mutation (70%)
1 inherited germline mutation + 1 spontaneous somatic mutation: "TWO-HIT MODEL"

G1-to-S TRANSITION

CDK4 CDK4 cyclinD cyclinE
Some proteins responsible for progression through transition and checkpoint.
ALL ARE CANCER GENES

Rb (retinoblastoma; EF2 inhibitor)
E2F (transcription factor)
p21 p53

degd dependent Cyclins are cyclin-dependent proteins that control the activity of other proteins by phosphorylating them.

BRCA example

"pRb was the first 'classic' tumor suppressor"

BRCA 1
(loc. = D17S74)
Ch 17

BRCA 2
(loc. = 13q/2-3)
Ch 13

The disease, retinoblastoma

Retinoblastoma is a cancer which develops in the cells of the retina
-one of the less common cancers of childhood
-accounts for only about 3 out of every 100 cancers occurring in children under the age of 15 years
Children present with:
an abnormal appearance of the pupil which reflects light as a white reflex, like a cat's eye.
a squint.

TUMOR-SUPPRESSOR GENE: Rb (Retinoblastoma)

(eye tumor example)

Inactive Transcription Factor, E2F

Gene expression; cell progression through cell cycle

Target gene

CDK enzymes: are cyclin-dependent protein kinases, control the activity of other proteins by phosphorylating them.
DOMINANT ONCOGENE
("GAIN-OF-FUNCTION" MUTATION)

- Mutant gene: Excessive protein or abnormally active protein ("always go")
- Normal gene

ONE MUTANT COPY AND IT IS A GO = DOMINANT

G2-to-M TRANSITION

CDC2, cyclinB, RAD9

Some proteins responsible for progression through transition and checkpoint.

ALL ARE CANCER GENES

ONCOGENE: RAS

HORMONE
Growth factor stimulates cell division

HORMONE + RECEPTOR

SIGNAL TRANSDUCTION CASCADE
G-PROTEIN: RAS oncogene signals whether or not hormone present

MAP kinase cascade

transcription factor stimulates growth

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)