Cancer: disease of transcription factors and replication

Uncontrolled cell growth and division

- immortalized cells
- tumor growth

- metastasis (cells float away from tumor and spread throughout the body), starting new tumors.

Cancer is caused by multiple mutations in the genes that code for proteins that regulate cell division.

Normally, small mutations fixed by DNA repair enzymes. If many mutations accumulate in a single cell, repair enzymes may be overwhelmed.

One out-of-control cell -> tumor.

Types of Cancers [-oma “growth”]

blastoma
malignancies in precursor cells, often called blasts, or incompletely differentiated precursor cells

sarcoma
derived from mesenchymal cells (middle layer of body: bone, cartilage, fat, muscle, vascular, or hematopoietic tissues)

carcinoma
derived from epithelial cells (tissues on inner or outer layer of the body: breast, skin, lung, colon, bladder )

germ cell tumor
testicular or ovarian cancers of germ cells

lymphoma and leukemia
hematopoietic cells, cancer cells found in lymph nodes (lymphoma) or blood (leukemia)

Density Dependent Inhibition

Cells anchor to dish surface and divide.

When cells have formed a complete single layer, they stop dividing (density-dependent inhibition).

If some cells are scraped away, the remaining cells divide to fill the gap and then stop (density-dependent inhibition).

Cancer cells do not exhibit density-dependent inhibition.
Phases of Tumor Growth

benign: circumscribed and localized neoplasm does not transform into cancer

pre-malignant (carcinoma in situ): Potentially malignant neoplasms that have not yet invaded or destroyed surrounding tissue

angiogenesis: growth or extension of new blood vessels into a tumor (or other tissue). Part of transition from benign to malignant tumor.

malignant (invasive): tumor invades and destroys the surrounding tissue, may form metastases

metastasis (displacement): spread of a cancer from one organ (primary tumor) to another non-adjacent organ (secondary tumor or metastatic tumor)

invasion: invasion of cancer cells through the basal membrane which surrounds vessels and into the blood or lymph

evasion: invasion of cancer cells from blood or lymph vessels into distant organ

Metastasis

Mechanisms of Cancer

1. Too much damage to cell’s DNA by environmental exposure.
   e.g. UV light, radiation, cancer-causing chemicals

2. Cancer-causing viruses

3. Genetic predisposition to cancer: an inherited mutation in a gene that
   a. regulates cell growth
   b. repairs DNA
Double-hit hypothesis:

Cancer occurs by a combination of these factors:
you have **two** copies of each growth gene and **both** copies need to be bad to start cancer.

(e.g. inherit one bad copy of a gene, and environmental exposure corrupts the other copy of the gene = **double-hit**)

Cancer is **probabilistic** -- but only one cell needs to become cancerous to generate tumor.
Double-Hit Hypothesis & Retinoblastoma

2 populations of patients: early tumors and later tumors

- Tumor in one eye (non-hereditary) gene is mutated in one cell in one eye shortly after birth.
- Tumor in both eyes (hereditary) mutated gene is inherited, so it's already in all cells in body, including both eyes.

[Graph showing age of diagnosis of retinoblastoma]

Cancer: A Disease of Aging

- 15-24 yr
- 25-44 yr
- 45-64 yr

[Graph showing cancer and other causes of death by age group]

“Health, United States 2003”, HHS

15-24 year olds

[Graph showing death rates per 100,000 population by cause]

“Health, United States 2003”, HHS
Three misfunctions due to genetic damage:

1. Increased activity of growth stimulator (accelerator stuck on)
2. Decreased activity of growth suppressor (brakes go out)
3. Decreased activity of DNA-repair enzymes

Which genes get damaged:

Proto-oncogenes
Genes that control cell growth or DNA repair in normal cells in a well-regulated way. If gene is damaged or taken over by a virus, the gene causes cancer.

Ras growth signal
(cut sarcoma gene)

Proto-oncogene: overactive growth signal causes cancer

P53 Tumor Suppressor

Defective expression of growth inhibitor causes cancer
Multiple gene mutations (e.g. loss of DNA repair enzymes) can speed up progression of cancer.

Three misfunctions due to genetic damage:
1. Increased activity of growth stimulator (accelerator stuck on)
2. Decreased activity of growth suppressor (brakes go out)
3. Decreased activity of DNA-repair enzymes

Which genes get damaged:

**Proto-oncogenes**
c-Fos
Genes that control cell growth or DNA repair in normal cells in a well-regulated way. If gene is damaged or taken over by a virus, the gene causes cancer.

Proto-oncogenes: not bad genes, just good genes gone bad.

c-FOS: Example of viral proto-oncogene
Causes Finkel Osteosarcoma bone cancer.

- **1930s** watch painters in New Jersey using radium paint had high levels of bone cancer.
- **1960s** virus isolated in bone cancer tumors.
- **1980s** viral gene product isolated - a transcription factor named v-Fos (viral FOS) that turns on cell growth genes.
- c-Fos - cellular gene normally expressed in cells. V-Fos missing sequence that degrades c-Fos after induction, so growth never turns off.

- **1990s** transgenic mice with too much c-Fos -> bone cancer.
  mice w/o c-Fos - underdeveloped bones.

Proto-oncogenes: not bad genes, just good genes gone bad.
c-FOS: Example of viral proto-oncogene

<table>
<thead>
<tr>
<th>C-Fos mRNA levels</th>
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<tr>
<td>Growth signal</td>
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<td>Viral Fos</td>
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<tr>
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A Continuation of The Journal of Cancer Research

VOLUME XV    OCTOBER, 1931    NO. 4

THE OCCURRENCE OF MALIGNANCY IN RADIOACTIVE PERSONS
A General Review of Data Gathered in the Study of the Radium Dial Painters, with Special Reference to the Occurrence of Osteogenic Sarcoma and the Inter-Relationship of Certain Blood Diseases

BARISON S. MARYLAND, M.D.
(From the Department of Pathology of the New York City Hospital and the Office of the Chief Medical Examiner of Essex County, New York, N. Y.)

21
“POISONERS! – as They Chatted Merrily at Their Work
Painting the Luminous Numbers on Watches, the Radium
Accumulated in Their Bodies, and Without Warning
Began to Bombard and Destroy Teeth, Jaws and Finger
Bones, Marking Fifty Young Factory Girls for Painful,
Lingering, and Inevitable Death.”

The drawing appeared p. 37 of the Hearst Sunday supplement
American Weekly, February 28, 1926 (Clark 14).

Over expression of c-Fos gene in transgenic mice
causes bone tumors
Deletion of c-Fos gene causes bone deformities

BRCA1 and BRCA2 mutations

Breast Cancer Associated Genes 1 and 2

Normal:
Estrogen + BRCA -> normal growth

Mutant:
Estrogen + mutant BRCA -> tumor growth

Mutation greatly increases cancer risk
Mutation is often present in certain high risk populations

BRAC mutation and Breast Cancer
BRAC mutation and Breast Cancer

- **Tumor growth**

- **BRCA1-RE**
  - Mutant BRCA1
  - Estrogen receptor gene

- **BRCA2**

- **Chromosome 17**
- **Chromosome 13**

BRCA1 Mutations

- Missense
- Deletion
- Insertion
- Homogeneous
Prevalence of BRCA1 Mutations

Higher in some populations:

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<thead>
<tr>
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<th>Ashkenazi Jews</th>
<th>Whole Population</th>
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<tbody>
<tr>
<td>185delAG</td>
<td>1%</td>
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<tr>
<td>5382insC</td>
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<td>1.4%</td>
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Risk associated with mutations:

Breast cancer: 1 in 9
Ovarian cancer: 1 in 70

by age 70, a woman with mutation has:
85% chance of breast cancer
44% chance of ovarian cancer.

But BRCA mutations present in only 7% of all cancers.

Cancer treatments

1. Kill rapidly dividing cells -- chemotherapy, radiation therapy.
   *Unfortunately, there are normal cells that rapidly divide e.g. in gut, hair cells, that are also killed.*

2. Block growth factors specific to tumors, or use drugs that specifically target tumor cells *(magic bullets).*

3. Molecular therapies: try to block or replace defective genes in tumor cells.
   *e.g., remove bone marrow, place in culture, fix mutated DNA in petri dish, put marrow back into the patient.*
What Is Metastasis?

When patients are diagnosed with cancer, they want to know whether their disease is local or has spread to other locations. Cancer spreads by metastasis, the ability of cancer cells to penetrate into lymphatic and blood vessels, circulate through the bloodstream, and then invade and grow in normal tissues elsewhere. In large measure, it is this ability to spread to other tissues and organs that makes cancer a potentially life-threatening disease, so there is great interest in understanding what makes metastasis possible for a cancerous tumor.

What Is Tumor Angiogenesis?

Tumor angiogenesis is the proliferation of a network of blood vessels that penetrates into cancerous growths, supplying nutrients and oxygen and removing waste products. Tumor angiogenesis actually starts with cancerous tumor cells releasing molecules that send signals to surrounding normal host tissue. This signaling activates certain genes in the host tissue that, in turn, make proteins to encourage growth of new blood vessels.

With Angiogenesis, Tumor Growth Proceeds

In another experiment designed to find out whether cancer growth can continue when angiogenesis occurs, researchers compared the behavior of cancer cells in two regions of the same organ. Both locations in the eye had nutrients available, but only one could support angiogenesis. Scientists found that the same starting injection of cancer cells grew to 1-2mm in diameter and then stopped in the region without nearby blood vessels, but grew well beyond 2 mm when placed in the area where angiogenesis was possible. With angiogenesis, tumor growth continued.