Cancer: disease of transcription factors and replication

1

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"]

2

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

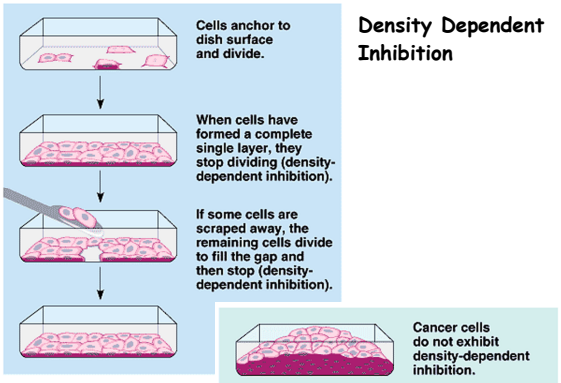
sarcoma
derived from mesenchymal cells (middle layer of body: bone, cartilage, fat, muscle, vascular, or hematopoietic tissues)

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)

3



Density Dependent Inhibition

Phases of Tumor Growth

4

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)

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

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

Metastasis

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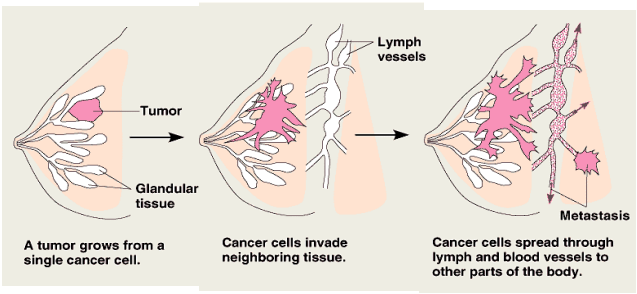

Mechanisms of Cancer

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1. Too much damage to cell's DNA by environmental exposure.

    e.g. UV light, radiation, cancer-causing chemicals

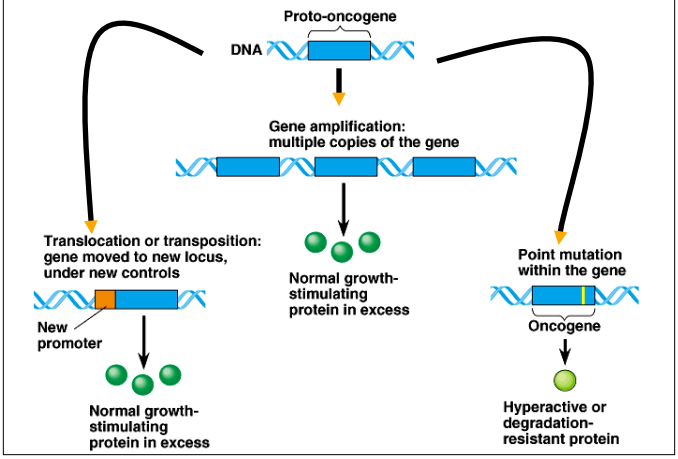
2. Cancer-causing viruses

3. Genetic predisposition to cancer: an inherited muation in a gene that

    a. regulates cell growth

    b. repairs DNA

Converting a normal gene into an oncogene



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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.

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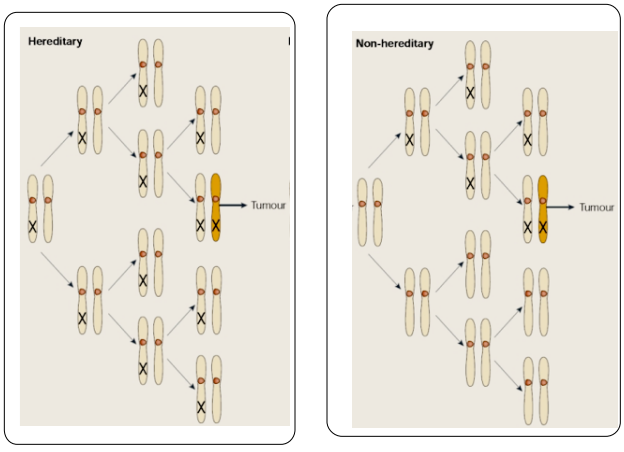
Two-Hit Hypothesis



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Double-Hit Hypothesis & Retinoblastoma
2 populations of patients: early tumors and later tumors

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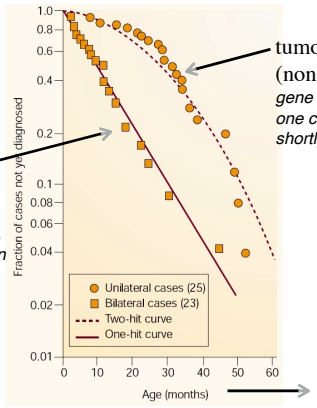
tumor in both eyes (hereditary)
mutated gene is inherited, so it's already in all cells in body, including both eyes



tumor in one eye (non-hereditary)
gene is mutated in one cell in one eye shortly after birth.

age of diagnosis of retinoblastoma

http://www.nature.com/scitable/topicpage/tumor-suppressor-ts-genes-and-the-two-887

Cancer: A Disease of Aging

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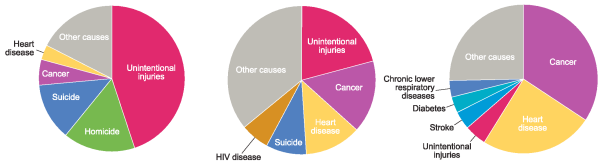

15-24 yr **25-44 yr** **45-64 yr**

"Health, United States 2003", HHS

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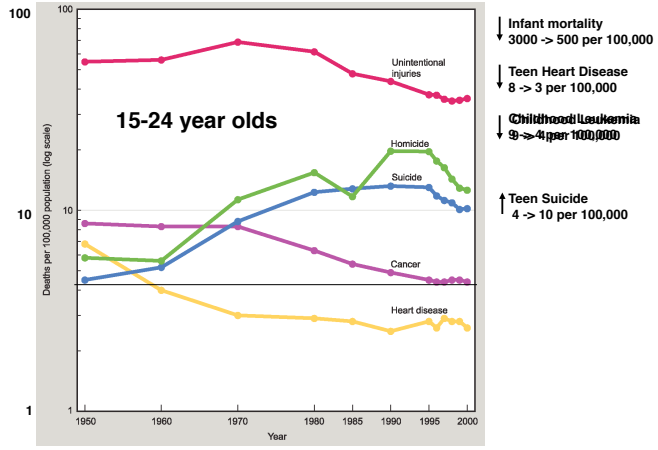

Infant mortality
3000 -> 500 per 100,000

Teen Heart Disease
8 -> 3 per 100,000

Childhood Leukemia
9 -> 4 per 100,000

Teen Suicide
4 -> 10 per 100,000

"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.

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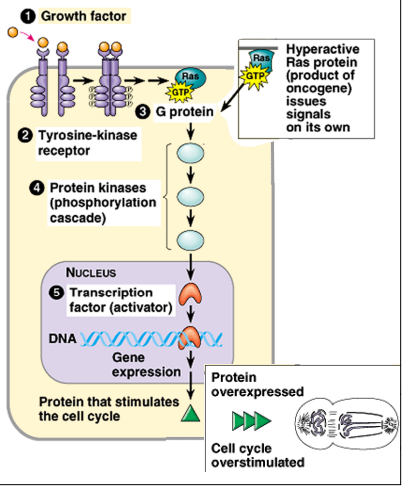
Ras growth signal

(rat sarcoma gene)

overactive growth signal causes cancer



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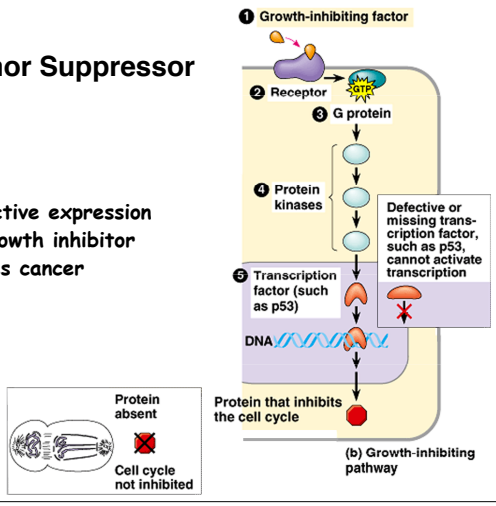
P53 Tumor Suppressor

defective expression of growth inhibitor causes cancer



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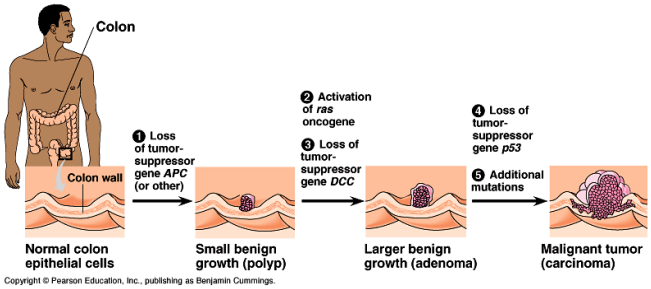
Multiple gene mutations (e.g. loss of DNA repair enzymes) can speed up progression of cancer.



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Three misfunctions due to genetic damage:

1. Increased activity of growth stimulator (accelerator stuck on) Ras
2. Decreased activity of growth suppressor (brakes go out)
3. Decreased activity of DNA-repair enzymes p53

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.

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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.

Protooncogenes: not bad genes, just good genes gone bad.

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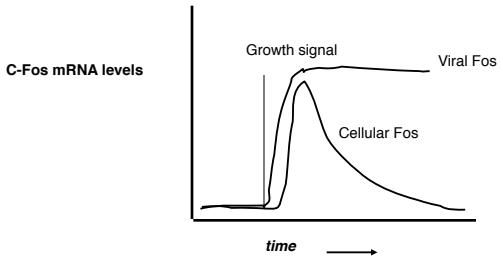
c-FOS: Example of viral proto-oncogene



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THE AMERICAN JOURNAL OF CANCER

A Continuation of The Journal of Cancer Research

VOLUME XV OCTOBER, 1931 No. 4

THE OCCURRENCE OF MALIGNANCY IN RADIO-ACTIVE 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

HARRISON S. MARTLAND, M.D.

(From the Department of Pathology of the Newark City Hospital and the Office of the Chief Medical Examiner of Essex County, Newark, N. J.)

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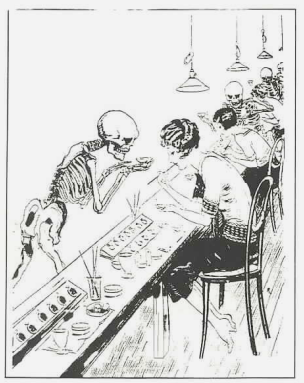

"POISONED! -- *as They Chatted Merrily at Their Work*

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, But Inevitable Death"

The drawing appeared on p. 11 of the Hearst Sunday supplement *American Weekly*, February 28, 1926 (Clark xiv).

www.gvsu.edu/english/ cummings/Him.htm

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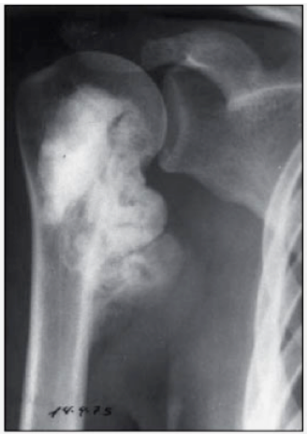

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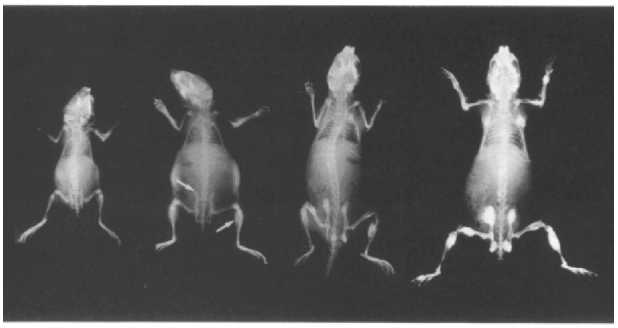
Over expression of c-Fos gene in transgenic mice causes bone tumors



2 weeks 4 weeks 9 weeks 14 weeks

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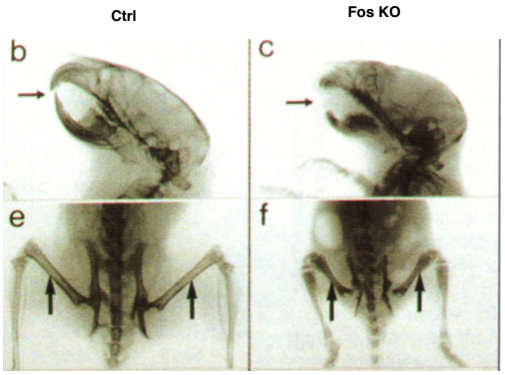
Deletion of c-Fos gene causes bone deformities



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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

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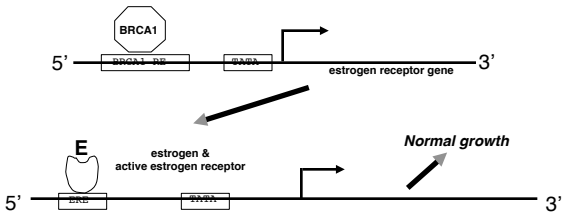
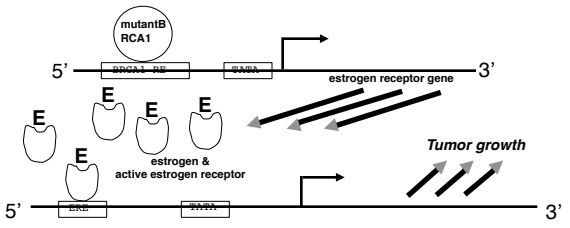
BRAC mutation and Breast Cancer



BRAC mutation and Breast Cancer



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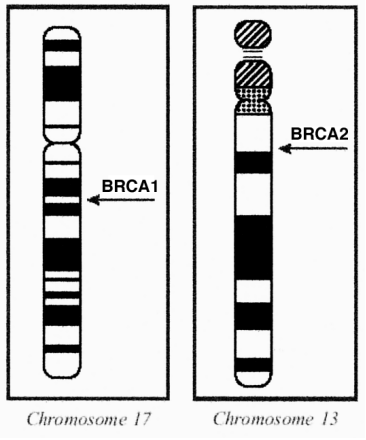

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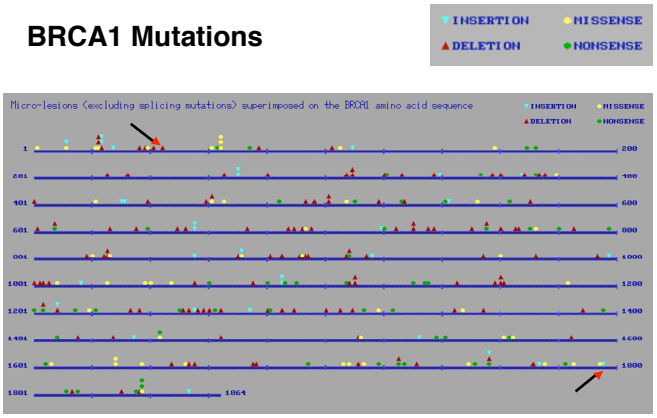
BRCA1 Mutations



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Prevelance of BRCA1 Mutations

Higher in some populations:

	Ashkenazi Jews	Whole Population
185delAG	1%	0.1%
5382insC	0.1%	1.4%

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.

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Lifetime BRCA1 and BRCA2 Cancer Risks for Women

Type of Cancer	Women with BRCA1 mutation	Women with BRCA2 mutation	Average woman in US without mutation
Breast	50-85%	50-85%	11%
Ovarian	20-40%	10-20%	1-2%
Colon	Possibly increased	Possibly increased	5-6%
Pancreatic	1%	2-3%	1%

Lifetime BRCA1 and BRCA2 Cancer Risks for Men

Type of Cancer	Men with BRCA1 mutation	Men with BRCA2 mutation	Average man in US without mutation
Breast	0.1%	6%	0.1%
Prostate	30%	20-30%	17%
Colon	Possibly increased	Possibly increased	5-6%
Pancreatic	1%	2-3%	1%

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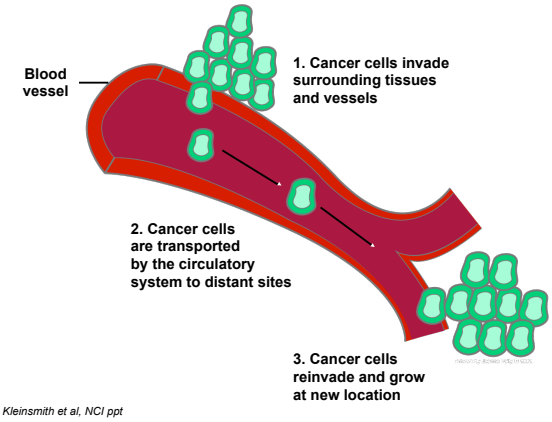
Cancer treatments

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?



Kleinsmith et al, NCI ppt

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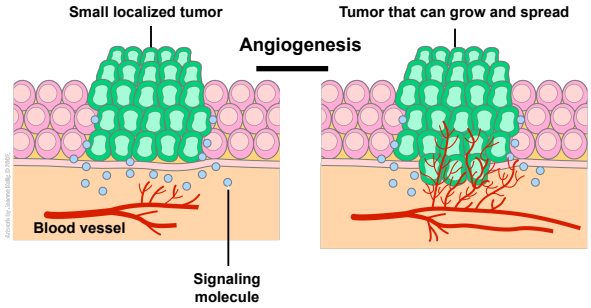
When patients are diagnosed with cancer, they want to know whether their disease is local or has spread to other locations. Cancer spreads by *metastasis*, the ability of cancer cells to penetrate into lymphatic and blood vessels, circulate through the bloodstream, and then invade and grow in normal 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?



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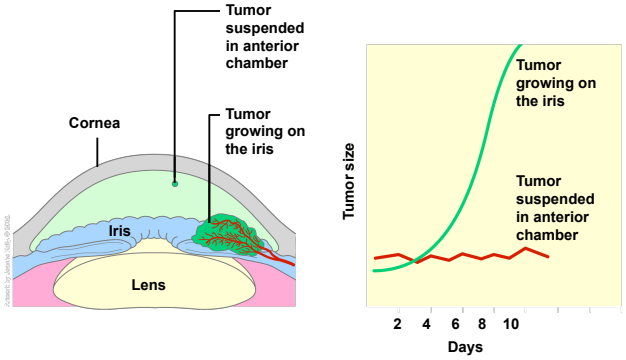
Tumor angiogenesis is the proliferation of a network of blood vessels that penetrates into cancerous growths, supplying nutrients and oxygen and removing waste products. Tumor angiogenesis actually starts with cancerous tumor cells releasing molecules that send signals to surrounding normal host tissue. 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



When tumor gets too big, it requires its own supply of blood vessels to bring nutrients and oxygen into the interior of the tumor.

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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.