

# Cancer Biology: The World Within a Cancer Cell

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## Disclosure

Dr. Dwinell is cofounder and a managing member of *Protein Foundry, LLC*, a biotech startup that manufactures recombinant chemokines for biomedical research.

Dr. Dwinell is the holder of US Patent #8,404,640 to treat malignant cancers with recombinant chemokines.

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## Outline

- **What is Cancer?**
  - Normal Cells versus Cancer Cells
  - Hallmarks of Cancer
- **Why do Cancers Grow?**
  - Unregulated Proliferation
  - Inhibited Cell Death
- **What is Metastasis?**
  - Increased Cellular Mobility
- **Cancers are Malignant Tissues**
  - Unique Tumor Microenvironments

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## What is Cancer?

- Tumors compromise the functioning of organs and give rise to symptoms...
  - Cancer cells possess 2 heritable characteristics:
    - 1- **reproduce** in defiance of normal restraints
    - 2- **invade** and **colonize** territories typically reserved for others
- **Primary Tumors:** account for 10% of all cancer deaths.
  - **Carcinoma:** arise from epithelial tissues
  - **Sarcoma:** arise from connective tissue or muscle
  - **Leukemia:** arise from hematopoietic or neural tissues
- **Secondary Tumors:** metastases responsible for 90% of cancer deaths.
  - **Metastasis** is specific movement of cancer cells to target organs
  - Extremely complicated & difficult process

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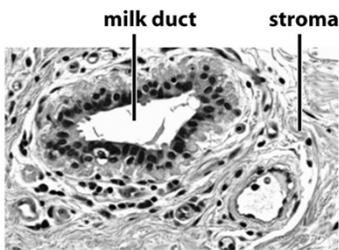
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## What is Cancer?

Normal



- Breast tissue is a collection of many different cell types, each with unique roles.
- Worn-out cells are replaced with new ones and there are checks and balances to maintain the correct number of healthy cells.

Weinberg, The Biology of Cancer

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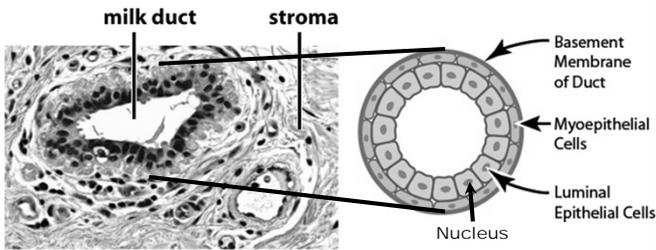
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## What is Cancer?

Normal



- The genes within each cells nucleus define what type of cell it will become and what roles it will carry out.

Weinberg, The Biology of Cancer

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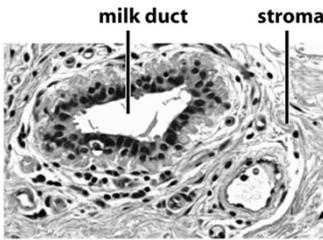
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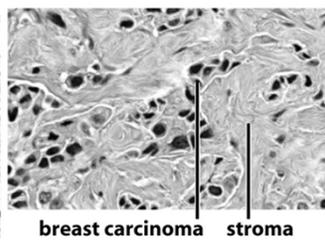
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## What is Cancer?

Normal



Cancer



- Mutations in genes within duct cells "unbalance" the normal cells checks and balances → UNCONTROLLED GROWTH
- Note too the change in stroma

Weinberg, The Biology of Cancer

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## What is Cancer?

- "Cancer: a collection of related diseases in which some of the body's cells begin to divide without stopping and spread into surrounding tissues."
  - 1) "...divide without stopping..."
    - UNCONTROLLED GROWTH
  - 2) "...spread into surrounding tissues."
    - INCREASED MOBILITY

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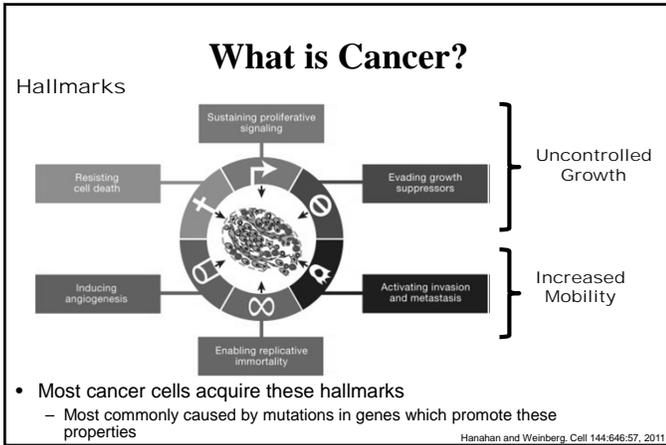
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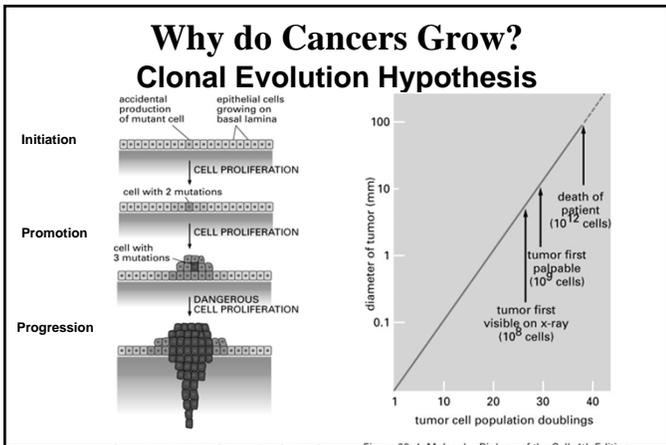
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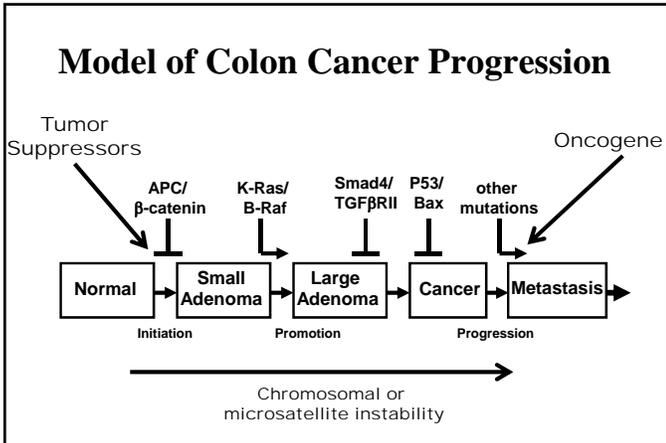
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### Why do Cancers Grow?

1. Genes Causing Cellular Dysregulation

- **Proto-oncogenes → Oncogenes**
  - Positive growth regulators
  - “Gain of function” mutation in one copy results in dominant active oncogene
  - Mechanisms of activation
    - Point mutations, gene amplification, translocation
  - Examples
    - Ras\*\*\*
    - BRAF\*\*\*
    - Src\*\*\*
    - Myc\*\*\*

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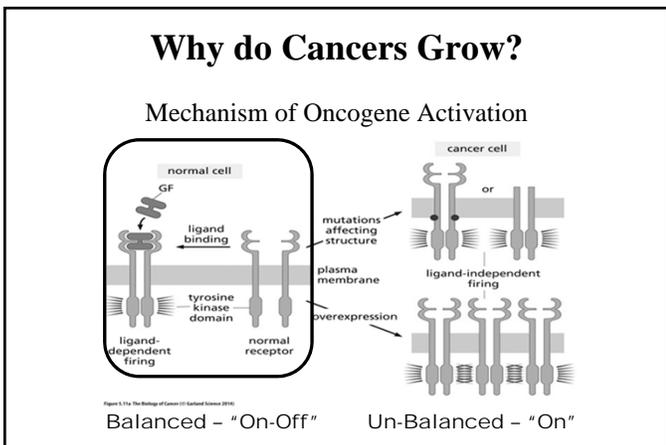
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## Why do Cancers Grow?

### 2. Genes Causing Cellular Dysregulation

- **Tumor Suppressor Genes**
  - Negative growth regulators
    - Inhibit proliferation, promote apoptosis, etc.
  - “Loss of Function” mutation in both alleles inactivates the gene product
  - Mechanism of inactivation
    - Loss of heterozygosity by mitotic recombination or chromosome mis-segregation
  - Examples
    - APC\*\*\*
    - p53\*\*\*
    - BRCA1/2

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## What is metastasis?

- **Metastasis:** the spread of cells from the primary neoplasm to growth in distant organs
- **Seed and Soil Hypothesis** (S. Paget, 1889)
  - “Metastasis was not due to chance (the prevailing viewpoint of that time), but that certain tumor cells ('seed') have specific affinity for the milieu of certain organs (the 'soil'). Metastases form only when the seed and soil are compatible.”
- Metastasis is an active and directed event. Tumor cells metastasize to defined tissues and is different for different kinds of cancers.

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## What is Metastasis?

### Metastasis is the result of genetic changes- Epithelial-Mesenchymal Transition

- Tumor invasion and metastasis mirrors normal embryogenesis and wound repair processes.
  - **EMT Model:** invasion & metastasis depends upon the reactivation of latent behavioral programs
  - Gene expression changes include: E-cadherin, plasminogen, MMPs, chemokine receptors

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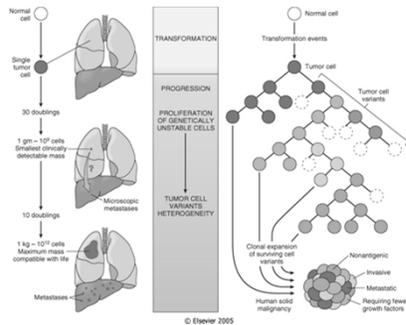
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## What is Metastasis?



- Metastasis reflects acquisition of gene mutations that promote cellular migration (increased locomotion)

Robbins, Pathologic Basis of Disease, 7th ed.

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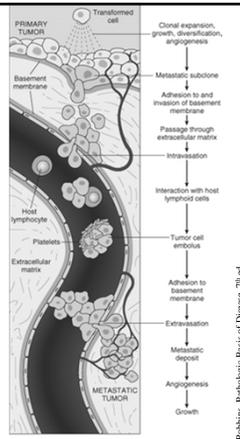
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## What is Metastasis?

1. Local invasion
2. Distant Spread
3. Metastatic Disease



Robbins, Pathologic Basis of Disease, 7th ed.

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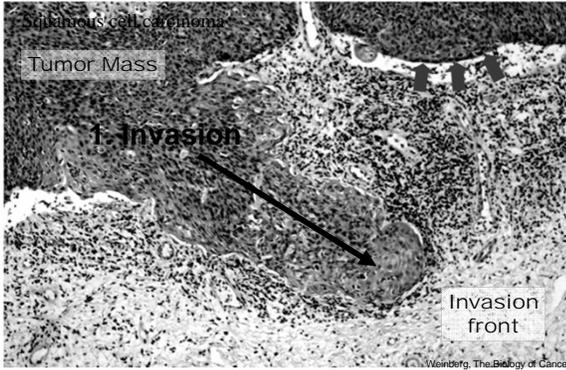
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## What is Metastasis?



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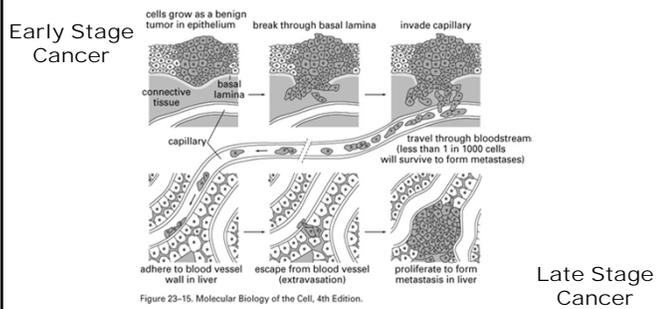
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## What is Metastasis?

### 2. Distant Spread



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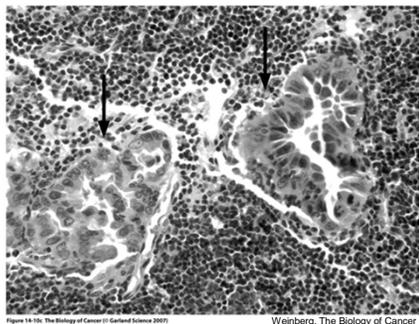
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## What is Metastasis?

### 3. Metastatic Disease

Cancer  
Micrometastases  
in Lymph Node



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## Cancers are Malignant Tissues

- **Malignant:**
  - adjective
  - 1. disposed to cause harm, suffering, or distress...
  - 2. very dangerous or harmful in influence or effect.
  - 3. **of a tumor:** characterized by uncontrolled growth; cancerous, invasive, or metastatic.
- **Tissue:**
  - Noun:
  - an aggregate of similar cells and cell products forming a definite kind of structural material with a specific function in a multicellular organism.

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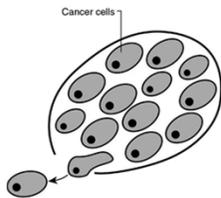
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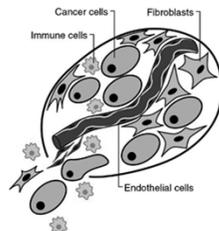
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## Cancers are Malignant Tissues

The Reductionist View



A Heterotypic Cell Biology



- Scientists and Physicians increasingly recognize that Cancer is NOT just about the cancer cell itself, but that the tumor cells exist within UNIQUE MICROENVIRONMENTS

Hanahan and Weinberg, Cell 144:646-57, 2011

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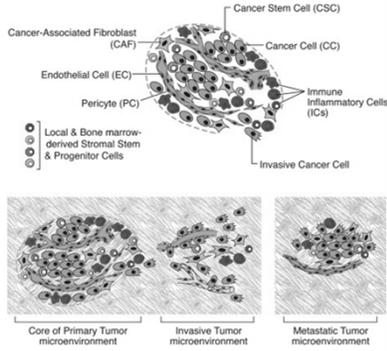
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## Cancers are Malignant Tissues

- Cancers are a collection of tumor cells (grey) surrounded by stromal and immune cells.
- These other cellular components are critical in uncontrolled growth and increased mobility
- Microenvironment also recognized as providing resistance to chemotherapy or radiotherapy interventions



Hanahan and Weinberg, Cell 144:646-57, 2011

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## Cancers are Malignant Tissues

- Microenvironment
  - In many cancers such as colon, breast, stomach, pancreas, the non-cancer cells (**STROMA**) may comprise 90% of the entire tumor mass
  - Change in fibroblasts surrounding the cancer cells
  - Tumor stroma may be BAD:
    - Growth signals
    - Block chemotherapy or radiation treatment
  - Tumor stroma may be GOOD:
    - Restrain invasion and metastasis

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## Cancers are Malignant Tissues

- Angiogenesis
  - Essential for progression of solid tumors to malignancy
  - Angiogenic factors include:
    - VEGF
    - Angiostatin

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## Cancers are Malignant Tissues

- Immune System (body's defense)
  - Immune system usually identifies and removes “non-self” and ignores “Self”
  - Several defense mechanisms against altered “Self” limits cancers
- Suppression
  - Factors produced by cancer cells or microenvironment leads to immune suppression, halt immune system reaction to the cancer cells

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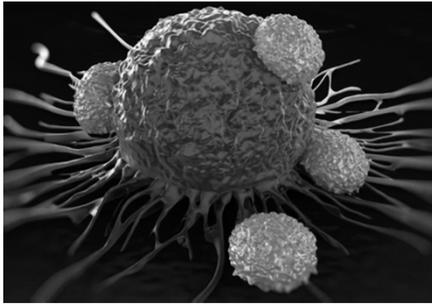
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## Cancers are Malignant Tissues

Targeting Immune  
Suppression  
Increasingly  
Effective  
Treatment



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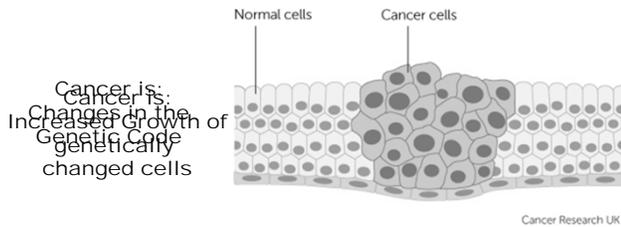
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## What is Cancer?




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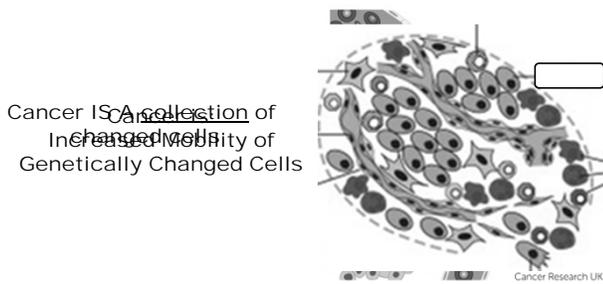
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## What is Cancer?




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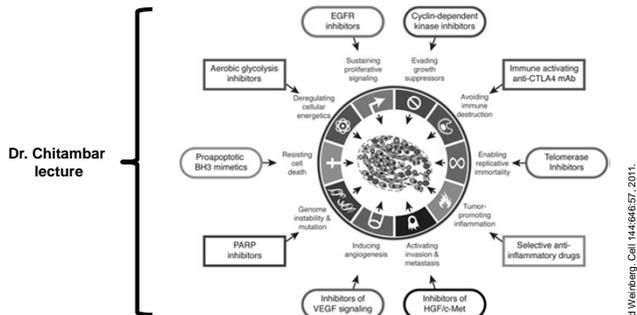
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## Cancers are Malignant Tissues



- Clinicians are increasingly targeting the Hallmarks of Cancer with specific chemotherapies in an attempt to thwart those tumorigenic processes.

Hosokawa and Weinberg, Cell 144:846-857, 2011.

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Thank you!

**Questions?**

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