Biology of Cancer

cancerquest.org

Characteristics of normal cell division

- Anchorage dependence
  - Cells must be attached to a solid surface to divide
- Density dependence
  - Cells stop dividing when too dense
- Growth factors
  - Signals that regulate cell cycle
- Senescence
  - After a finite # divisions, cell self-destruct (**apoptosis**)
    - Irreparable DNA or membrane damage
    - Shortened telomeres

Primary culture of normal cells

- **Growth factor dependence**

EXPERIMENT

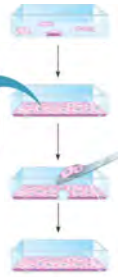
1. A sample of connective tissue was cut up into small pieces.
2. Enzymes were used to digest the extracellular matrix, resulting in a suspension of free fibroblast cells.
3. Cells were transferred to sterile culture vessels containing a basic growth medium consisting of glucose, amino acids, salts, and antibiotics (as a precaution against bacterial growth).
   PDGF (platelet-derived growth factor) was added to half of the vessels (T-flasks).
   The culture vessels were incubated at 37°C.
4. Cells cultured without PDGF did nothing.
   Cells cultured **with** PDGF attached to the vessel, flattened out, and began dividing. **[Growth-factor dependent growth]**

Figure 12.17

Primary culture of normal cells

- **Anchorage dependence; Density-dependent inhibition; & Senescence**

4. Cells cultured **with** PDGF attached to the vessel, flattened out, and began dividing. **[Growth-factor dependent growth]**
   Cells anchor to dish surface and divide. **[anchorage dependence]**
   When cells have formed a complete single layer, they stop dividing. **[Density-dependent inhibition]**

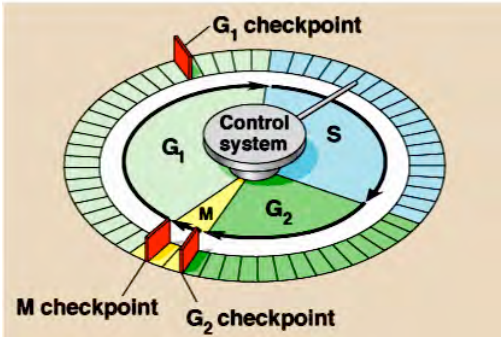


   If some cells are scraped away, the remaining cells divide to fill the gap and then stop. **[Density-dependent inhibition]**
5. But even with low cell density, available surface, and added growth factors, after 20–50 cycles, the cells stop dividing, ball up, and detach. **[Senescence]**

Figure 12.18 A

Cell Cycle Checkpoints

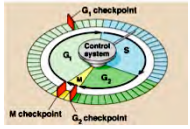
Assures key processes are completed before cycle progresses



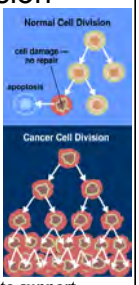
Cell Cycle Checkpoints

Assures key processes are completed before cycle progresses

- **G_1 checkpoint:**
  - ✓ Sufficient growth & reserves to support replication
  - ✓ Pre-replication check for DNA damage
  - ✓ Internal clock
  - ✓ External growth factors and/or inhibitors
- **G_2 checkpoint:**
  - ✓ Sufficient growth & reserves to support mitosis & cytokinesis
  - ✓ Duplication of centrosomes
  - ✓ Replication of DNA
  - ✓ Pre-mitotic check for DNA damage
- **M checkpoint**
  - ✓ Spindle formed & functioning
  - ✓ Chromosome kinetochores correctly attached to spindle
  - ✓ Chromosomes properly aligned & untangled on metaphase plate



Transformation: damage to checkpoint mechanisms cause abnormal cell division



"**Hallmarks of Cancer**":

- Growth independent of external growth regulators
  - Loss of anchorage & density dependence
  - Uncoordinated with surrounding tissues or the body
- Growth without stopping at checkpoints
- Avoidance of apoptosis despite cell/DNA damage
- Unlimited number of cell divisions
  - Activation of telomerase

Other indicators:

- De-differentiation
- Δ cytoskeleton → Δ morphology & motility
- Angiogenesis — induced growth of blood vessels to support increased metabolic demands of hyper-growth

Primary culture of *transformed* cells

- **Cancer cells exhibit neither density-dependent inhibition nor anchorage dependence**
- **And have only limited dependence on growth factors**

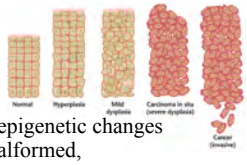
Cancer cells usually continue to divide well beyond a single layer, forming a clump of overlapping cells.

Many transformed cell lines can also be cultured as liquid cell suspensions with no need for attachment substrate.

Figure 12.18 B

- **Transformed cells are also *immortalized* — showing no senescence**
  - E.g., the HeLa cell line was cultured from a tumor removed from Henrietta Lacks back in 1951. It is still growing in labs all over the world.

Stages of tumor progression



1. **Hyperplasia**: over-production of normal-looking cells.
2. **Dysplasia**: additional genetic/epigenetic changes lead to abnormal growth of malformed, disorganized cells.
3. **Solid tumor *in situ***: cells are even more malformed and de-differentiated. Growth extends from original mass into the tissue.
4. **Malignancy (cancer)**: cells detach and penetrate basal lamina into other tissues. May enter lymphatic or circulatory system and reach other organs to start new tumors.

Stages of tumor progression

- Metastasis: spread of malignant cells from original tissue

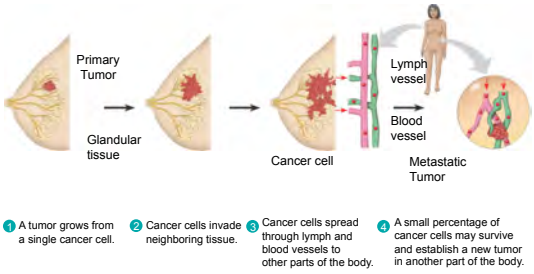
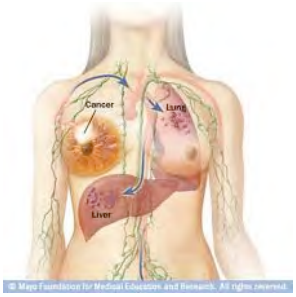


Figure 12.19

Stages of tumor progression

- Metastasis: spread of malignant cells from original tissue



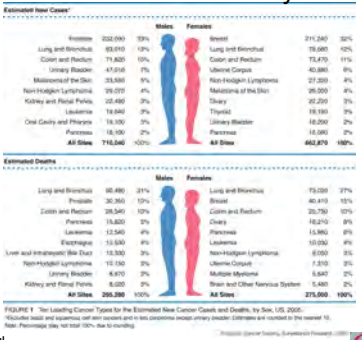
Types of tumors

Classification based upon tissue of origin

- "Solid tumors"
  - **Carcinoma**: epithelial cells
    - 80–90% of all cancers
  - **Sarcoma**: muscle or connective tissue
- Others
  - **Leukemia/Lymphoma/Myeloma**: bone marrow
  - **Glioma**: brain
  - **Choriocarcinoma**: placenta

Pulmonary carcinoma *in situ*

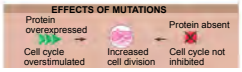
Cancer incidence & mortality in the U.S.



From Jemal, A. et al.
CA Cancer J Clin 2005;55:10-30.

Transformation requires a **series** of non-lethal mutations within a specific cell line

- Turn on "on-switches"
  - Dominant mutations: proto-oncogenes ⇒ **oncogenes**
  - Bypass checkpoints
- Turn off "off-switches"
  - Recessive mutations: inactivate **tumor suppressors**
  - Remove checkpoints
- All cancers involve mutations in one or more oncogene and one or more tumor suppressors.



Sources of mutations

- Spontaneous
- Induced — mutagens/carcinogens
  - Radiation
    - UV — mostly point mutations
    - X-rays — translocations
  - Endogenous chemicals
    - Reactive oxygen species (ROS) → alter DNA bases
      - Chronic inflammation
      - Fat metabolism
  - Exogenous chemicals
    - Bind to DNA → replication & transcription errors
      - Benzo-pyrene from tobacco smoke
      - Aflatoxins from food-borne fungi
  - Viruses
    - Inserted pro-viruses
    - Viral-induced growth factors
    - Genetic carry-over from prior host cells

World Health Organization

Cancer Fact Sheet

http://www.who.int/mediacentre/factsheets/fs297/en/
Fact sheet N°297; Updated February 2015

- **Cancers** figure among the **leading causes of morbidity and mortality** worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012.
  - The number of new cases is expected to **rise** by about 70% over the next 2 decades. [to 22 million]
- Around **one third** of cancer deaths are due to the 5 leading **behavioral and dietary risks**: tobacco use, obesity, low fruit and vegetable intake, lack of physical activity, alcohol use.
- **Tobacco** use is the **most important risk factor** for cancer causing around 20% of global cancer deaths and around 70% of global lung cancer deaths.
  - Tobacco-related cancers, combined with tobacco-related diseases including cardiovascular and chronic lung diseases, make **tobacco use the leading cause of preventable deaths in the world**. [Even without effects of 2nd- & 3rd-hand smoking.]

Oncogenes

- **Proto-oncogene**: normal gene functions in stimulating cell growth or viability, esp. for embryogenesis & organogenesis.
- Mutated form = **oncogene**: stimulates unregulated cell division or immortalization.
- Presence of the oncogene or oncogene product ⇒↑probability of transformation

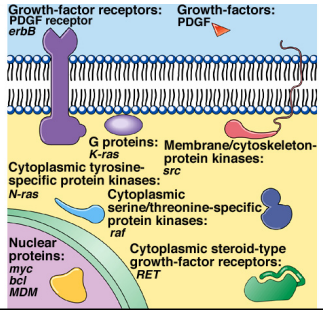
Oncogenes

- Presence of the oncogene or oncogene product ⇒↑probability of transformation
- **Types of oncogenes:**
  - Growth factors
  - Growth factor receptor (HER2)
  - G-proteins (Ras)
  - Receptor-associated kinases (Src)
  - Transcription factors (Myc)
  - Telomerase activators
  - Apoptosis-regulating proteins (Bcl-2)

Oncogenes

- Mutated proto-oncogenes may become oncogenes — tell cells to proliferate inappropriately.

Main Classes of Onco-genes



Genetic changes that can turn proto-oncogenes into oncogenes

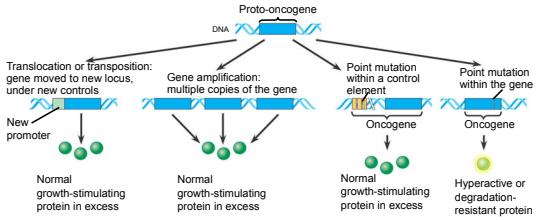


Figure 18.23

Ras

Mutation of ***ras*** proto-oncogene identified in ~30% of human cancers.

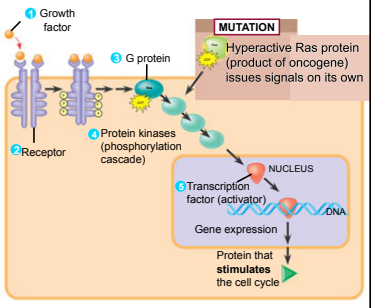


Figure 18.24

Tumor suppressors

- **Tumor suppressors**: normal gene functions in delaying cell growth, locating or repairing damaged DNA, or initiating apoptosis of irreparably damaged or senescent cells.
- Mutated form is inactive: unable to regulate cycle, detect or repair genetic damage, or divert to self-destruct.
- Absence of the tumor suppressor ⇒↑probability of transformation

Tumor suppressors

- Absence of the tumor suppressor ⇒↑probability of transformation
- **Types of tumor suppressors:**
  - Transcription factors (p53)
  - Factors that restrict access of transcription factors (APC)
  - Factors that block effects of transcription factors (Rb)
  - DNA repair (BRCA)

p53 Tumor suppressor

Mutation of ***p53*** tumor suppressor identified in >50% of human cancers.

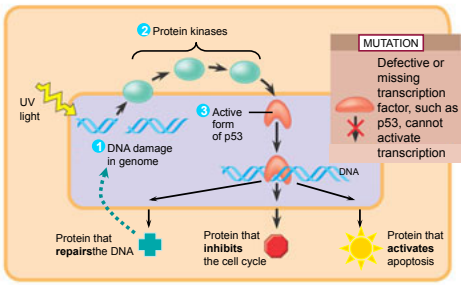
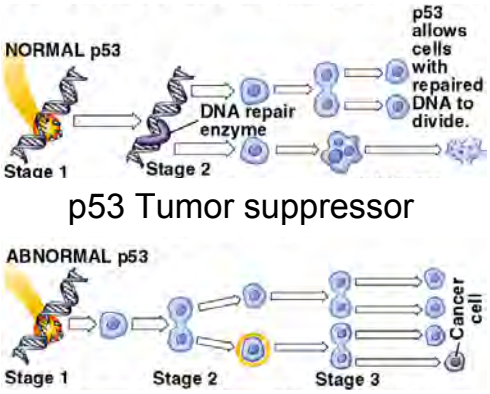
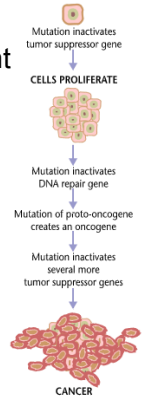


Figure 18.25



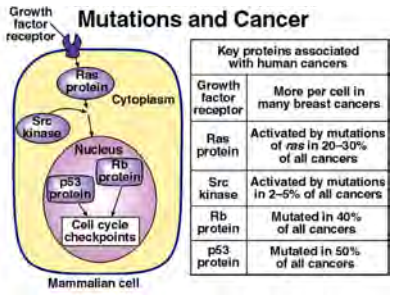
Clonal evolution (multistep) model of cancer development

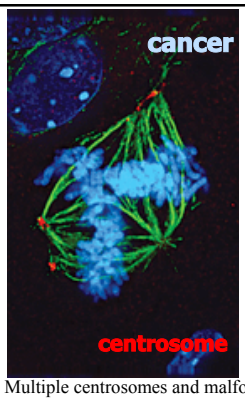
1. Point mutations in tumor suppressor gene allows cell divisions without adequate checks & repair of DNA damage
2. Aberrant cell divisions result in further genetic damage, including translocations, deletions, and aneuploidy.
3. Major genetic rearrangements create further disruptions of proto-oncogenes and tumor suppressors to produce transformation and further stages of tumor progression.



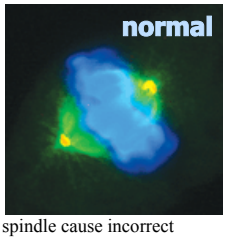
Multistep model of cancer development

- Carcinogenesis requires both oncogene and tumor suppressor mutations.

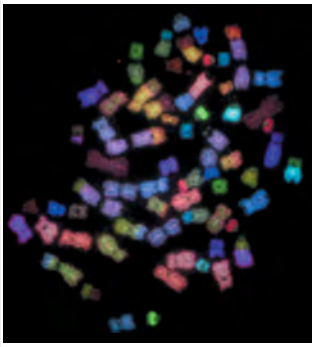




Aberrant cell division causes genetic disruption



Multiple centrosomes and malformed spindle cause incorrect distribution of chromatids to daughter cells. [Science 292: 427 (2001)]



Aneuploidy and other chromosome changes are common in cancer cells.

- Most [all?] cancer cells are aneuploid.
- Many have >100 chromosomes/cell!

Aneuploid lung cancer cell
[Nature 432, 338 - 341 (18 November 2004)]

A multistep model for the development of colorectal cancer

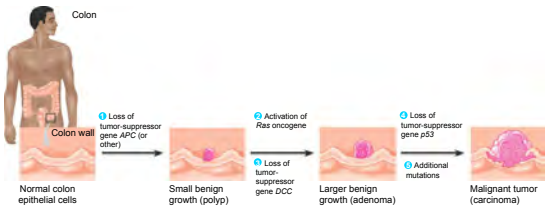
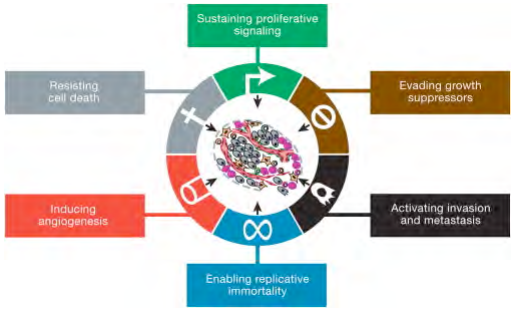


Figure 19.13

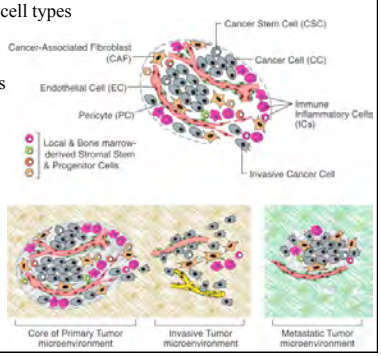
The Hallmarks of Cancer



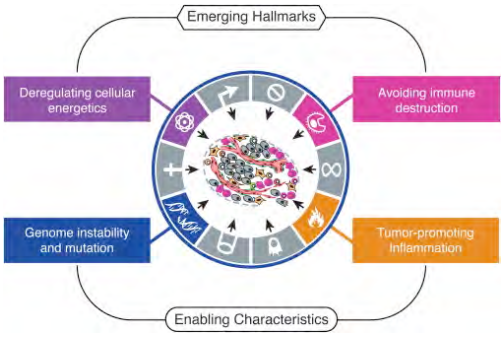
Hallmarks of Cancer: The Next Generation
Douglas Hanahan, Robert A. Weinberg
Cell - 4 March 2011 (Vol. 144, Issue 5, pp. 646-674)

The Tumor as an Organ

- Mixed population of cell types
- Cancer cells recruit and alter activity of non-transformed cells

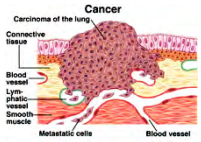


Additional "Emerging Hallmarks" and Enabling Characteristics of progressing tumor



What is cancer?

1. Unrestricted proliferation of a cell line
   - Displacement of healthy tissues
   - Pressure on confined tissues
   - Over-consumption of resources
2. Metastasis
   - Spreading
3. Disrupted gene expression
   - De-differentiation
   - Loss of normal function
   - Inappropriate production of bioactive substances



Therapeutic Targeting of the Cancer "Hallmarks"