What is Cancer?

• Cancer is a genetic disease:
  – Inherited cancer
  – Sporadic cancer

• Cancer typically involves a change in gene expression/function:
  – Qualitative change
  – Quantitative change

• Any cancer causing genetic alteration typically results in loss of cell growth control.
What is Cancer?
What is Cancer?
Malignant Vs. Benign growth

• **Benign**: called a tumor
  – Well circumscribed, slow growing, non invasive, non metastatic.

• **Malignant**: called a cancer
  – Not well organized, irregularly shaped, fast growing, infiltrative growth, metastatic.

• Initial stages of malignant cancer may typically show benign growth;
  – further accumulation of mutations may make it malignant.
Benign Vs. Malignant Tumors

- Benign tumors are tumors that cannot spread by invasion or metastasis; hence, they only grow locally.

- Malignant tumors are tumors that are capable of spreading by invasion and metastasis.

- By definition, the term "cancer" applies only to malignant tumors.

Cancer: Loss of Cell Growth Control

- Cancer arises from a loss of normal growth control.
- In normal tissues, the rates of new cell growth and old cell death are kept in balance.
- In cancer, this balance is disrupted. This disruption can result from uncontrolled cell growth or loss of a cell's ability to undergo "apoptosis."
- Apoptosis, or "cell suicide," is the mechanism by which old or damaged cells normally self-destruct.

Loss of Cell Cycle Regulation at Checkpoints

- Accumulation of DNA damage, errors in replication, introduction of mutations, chromosomal translocations, aneuploidies
- Increased growth rate, escape from apoptosis

Tumor Cell Formation

Normal Cell → Tumor Cell
Properties of Cancer Cells

• Cancer cells exhibit several characteristics that are distinct from normal cells.

• Multiple changes are involved in the conversion of a normal cell to a cancer cell:
  – Autocrine stimulation; grow in the absence of growth factors
  – Lack of gap junctions;
  – lack of contact inhibition
  – Resistance to cell death; persistent telomerase activity
  – Rapid growth; overtake population, invade other tissues.
  – Angiogenesis
  – Clonal nature of cancer
  – Genomic Instability: Accumulation of successive mutations

• A germline mutation causes a hereditary cancer.

• A somatic mutation causes a sporadic cancer.
Properties of Cancer Cells: Autocrine stimulation, Lack of contact inhibition, Lack of cell death, Lack of gap junctions
Properties of Cancer Cells: Lack of contact inhibition

Normal skin cells
Grow in monolayer

Skin cancer cells
Do not grow in monolayer
Pile up on each other
Properties of Cancer Cells: Lack of Apoptosis (Programmed cell death)
Properties of Cancer Cells: Genomic Instability

- Replication
- Mismatch created by DNA polymerase
  - Normal cell — corrected by mismatch repair
  - Mismatch not corrected in cancer cell
- Replication
- Mutation
Properties of Cancer Cells:
Changes that produce a potential for immortality

- Loss of limitations on the number of cell divisions
- Ability to grow in culture – normal cells do not grow well in culture
- Restoration of telomerase activity

Feature Figure 18.16 c
Properties of Cancer Cells:
Changes that enable tumor to disrupt local tissue and invade distant tissues

- Ability to metastasize
- Angiogenesis – secrete substances that cause blood vessels to grow toward tumor
- Evasion of immune surveillance
Properties of Cancer Cells: clonal descendents of one cell

X<sup>A</sup>X<sup>B</sup> Female

Tumor

Sample of tissue

Clone 1 of cells

Clone 2 of cells

Electrophoresis to separate allelic forms of enzyme

Tissue sample

Clone 1 of normal cells

Clone 2 of normal cells

Tumor sample

Fig. 18.18
Most cancers result from exposures to mutagens

- If one sib or twin gets cancer, other usually does not
- Populations that migrate – profile of cancer becomes more like people indigenous to new location

**TABLE 18.2 The Incidence of Some Common Cancers Varies Between Countries**

<table>
<thead>
<tr>
<th>Site of Origin of Cancer</th>
<th>High-Incidence Population</th>
<th>Incidence*</th>
<th>Low-Incidence Population</th>
<th>Incidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>USA (New Orleans, blacks)</td>
<td>110</td>
<td>India (Madras)</td>
<td>5.8</td>
</tr>
<tr>
<td>Breast</td>
<td>Hawaii (Hawaiians)</td>
<td>94</td>
<td>Israel (non-Jews)</td>
<td>14.0</td>
</tr>
<tr>
<td>Prostate</td>
<td>USA (Atlanta, blacks)</td>
<td>91</td>
<td>China (Tianjin)</td>
<td>1.3</td>
</tr>
<tr>
<td>Cervix</td>
<td>Brazil (Recife)</td>
<td>83</td>
<td>Israel (non-Jews)</td>
<td>3.0</td>
</tr>
<tr>
<td>Stomach</td>
<td>Japan (Nagasaki)</td>
<td>82</td>
<td>Kuwait (Kuwaitis)</td>
<td>3.7</td>
</tr>
<tr>
<td>Liver</td>
<td>China (Shanghai)</td>
<td>34</td>
<td>Canada (Nova Scotia)</td>
<td>0.7</td>
</tr>
<tr>
<td>Colon</td>
<td>USA (Connecticut, whites)</td>
<td>34</td>
<td>India (Madras)</td>
<td>1.8</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Australia (Queensland)</td>
<td>31</td>
<td>Japan (Osaka)</td>
<td>0.2</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>Hong Kong</td>
<td>30</td>
<td>UK (southwestern)</td>
<td>0.3</td>
</tr>
<tr>
<td>Esophagus</td>
<td>France (Calvados)</td>
<td>30</td>
<td>Romania (urban Cluj)</td>
<td>1.1</td>
</tr>
<tr>
<td>Bladder</td>
<td>Switzerland (Basel)</td>
<td>28</td>
<td>India (Nagpur)</td>
<td>1.7</td>
</tr>
<tr>
<td>Ovary</td>
<td>New Zealand (Polynesian Islanders)</td>
<td>26</td>
<td>Kuwait (Kuwaitis)</td>
<td>3.3</td>
</tr>
<tr>
<td>Pancreas</td>
<td>USA (Los Angeles, Koreans)</td>
<td>16</td>
<td>India (Poona)</td>
<td>1.5</td>
</tr>
<tr>
<td>Lip</td>
<td>Canada (Newfoundland)</td>
<td>15</td>
<td>Japan (Osaka)</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Cancer develops over time

Males began frequent smoking after 1940

Females began frequent smoking after 1960
Cancer develops over time

Mutations accumulate over time
Incidence of cancer increases with age

Fig. 18.19
Sporadic Vs. Familial Cancer

• **Familial:**
  • inherited form. The family has a predisposition through a germline mutation.
    – Increases the probability that further mutations will occur.
    – Sometimes the initial germline mutation may be responsible for different cancers:
      • e.g. same family may have individuals with breast, bone, lung, ovarian cancer because of a single inherited germline mutation:
        • e.g.: *p53*.

• **Sporadic cancers:**
  • new mutations arising in somatic cells of the body.
    – Could result in any type of cancer, depending on the where the mutation occurs.
Familial Cancer

Inheritance of a mutation in a "cancer protection" gene in a germ cell (egg or sperm). The offspring will have both a faulty copy and a correct copy of the "cancer protection" gene in all the cells of their body, and will be predisposed to develop cancer.

From: The Center for Genetics Education Website: http://www.genetics.com.au/
Sporadic Cancer

Mutations that occur during life in the body cells (somatic mutations) such as the cells of the breast are confined to the breast tissue. These mutations will not be passed on to the next generation.

From: The Center for Genetics Education Website: http://www.genetics.com.au/
Genes and Cancer

• Two classes of genes are mutated frequently in cancer:

  – **Tumor suppressor genes**: loss of function mutations.
    • Normal function is to **prevent** cell proliferation.
    • So-called “cancer protection” genes

  – **Protooncogenes**: gain of function mutations.
    • quantitative change in expression of these genes common in cancer
    • Normal function is to **promote** cell proliferation.
Tumor Suppressors vs. Oncogenes

- **Oncogenes**
  - dominant mutations

- **Mutant tumor-suppressor genes**
  - recessive mutations
Mutations to proto-oncogenes

Proto-oncogene (such as Her2) → DNA → Protein

Mutated proto-oncogene (oncogene) → Mutation → Protein

- Functional protein only stimulates cell division when conditions are right.
- Mutated protein can lead to overstimulation of cell division by overriding checkpoint control.
Mutations to tumor suppressor genes

**Tumor suppressor** (such as BRCA2)

Tumor-suppressor protein stops tumor formation by suppressing cell division.

**Mutated tumor suppressor**

Mutation

Mutated tumor-suppressor protein fails to stop tumor growth.

Figure 5-14b Biology: Science for Life, 2/e © 2007 Pearson Prentice Hall, Inc.
**Multistep Nature of Cancer**

- Cancer develops progressively as mutations accumulate.

- Experimental evidence in mice with either the *ras* OR the *myc* protooncogenes mutated: fewer tumors develop than when BOTH genes are mutated.

- Mice with only one allele of the tumor suppressor *p53* mutated are not as cancer prone as when both alleles are mutated.

- Hereditary adenomatous polyposis or Familial adenomatous polyposis (FAP):
  - a typical example of the multi-step pathway for cancer.
Multistep Nature of Cancer

Normal cell

First mutation

Second mutation

Third mutation

Fourth mutation

Malignant cell
The Multi-Step Model for Colon Cancer

- Tumor suppressor genes: $APC$, $DCC$, $p53$
- Oncogene: $ras$

1. Normal colon cells
2. $APC$ gene loss
3. Increased cell growth
4. DNA hypomethylation
5. Adenoma class I
6. $ras$ gene mutation
7. $DCC$ gene loss
8. Adenoma class II
9. $p53$ gene loss
10. Carcinoma
11. Other gene losses
12. Metastasis
The Multi-Step Model

(a) Colon cancer

- Loss of *apc* gene (chromosome 5)
- Oncogenic mutation of a *ras* gene (chromosome 12)
- Loss of *p53* gene (chromosome 17)
- Loss of a gene (possibly *dcc*) on chromosome 18

(b) Astrocytoma

- Loss of *p53* gene
- Loss of a cluster of genes on chromosome 9
- Loss of one copy of chromosome 10

Normal colonic mucosa | Benign (early) adenoma | Benign (late) adenoma | Malignant invasive carcinoma
Normal tissue | Low-grade tumor | Higher-grade tumor | Most aggressive form of tumor
Genomic Approaches to Cancer Diagnostics and Therapies

• Cancer Diagnostics Goal:
  • Properly classify the type of cancer
  • To properly treat that specific type
    • Usually done by morphology,
    • Certain tumor surface markers,
    • and Identification of translocations

• Now, genomic approaches can help
  • Determine the gene expression array of the tumor
  • Compare to tumors with known patient outcome
  • Gene profiling

• Example: Non-Hodgkin Lymphoma, DLBCL
Non-Hodgkin Lymphoma, DLBCL

(a) Normal B lymphocytes

(b) Diffuse Large B Cell Lymphoma
Non-Hodgkin Lymphoma, DLBCL

Higher patient survival rate correlates with GC B-like RNA profile
Homework

• Chapter 22

• # 15, 16,