Papers for Discussion (Nov-22)


Overview of M Phase

<table>
<thead>
<tr>
<th>A. Interphase</th>
<th>B. Prophase</th>
<th>C. Prometaphase</th>
<th>D. Metaphase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleus</td>
<td>Centrosome</td>
<td>Nuclear envelope (NE) breaks down</td>
<td>Chromosomes align on spindle equator</td>
</tr>
<tr>
<td>Microtubules</td>
<td>Chromosomes separate</td>
<td>Chromosomes condense</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E. Anaphase A</th>
<th>F. Anaphase B</th>
<th>G. Telophase</th>
<th>H. Cytokinesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sister chromatids separate and move to poles</td>
<td>Organized central spindle (CS) assembles</td>
<td>Cleavage furrow (CF) assembles</td>
<td>Chromosomes decondense</td>
</tr>
<tr>
<td></td>
<td>Cleavage furrow (CF) assembles</td>
<td>Cleavage furrow (CF) constricts</td>
<td>Interphase microtubule network reforms</td>
</tr>
<tr>
<td></td>
<td>Poles (arrow) separate</td>
<td>Nuclear envelope (NE) reassembles</td>
<td>Daughter cells separate</td>
</tr>
</tbody>
</table>
Anaphase A

• Movement of sister chromatids to the poles requires shortening of kinetochore MTs.

• Anaphase A follows activation of APC/C^{Cdc20}.

• After spindle checkpoint is turned off, APC/C^{Cdc20} triggers the degradation of securin.

• Reduced securin level allows separase to cleave cohesin.
Anaphase B

- Spindle elongation pushes spindle poles apart in Anaphase B.

- Chromosome movement is driven by two factors
  - microtubule shortening and growth
  - microtubule flux

- Spindle elongation
  - Antiparallel sliding of microtubules
  - Microtubule growth
  - Spindle pole motility
Telophase

• Nuclear envelope starts to reassemble in late anaphase and is completed in telophase.

• Ran-GTP mediates nuclear envelope assembly.

• Nuclear lamina reassembles through recycling of disassembled lamin subunits.
Cytokinesis (I)

- Two daughter cells become separated through cytokinesis.
- Formation of the contractile ring requires actin and myosin-II.
- Separation of two daughter cells is accompanied by constriction and disassembly of the contractile ring.
Cytokinesis (II)

- Cytokinesis requires membrane addition and abscission.
- Secretory vesicles from the Golgi provides new membrane.
- Midbody contains many proteins involved in membrane trafficking.
- Intracellular bridges may remain open to connect cells.
Exit From Mitosis

- Cdk1 must be inactivated for exit from mitosis.
- Much of what is known of exit from mitosis comes from budding yeast.
- Exit from mitosis in yeasts is mediated by the MEN GTPase.
- Lowered Cdk activities allow the release of MEN GTPases.
- Released MEN GTPases activate Cdc14p, which inhibits Cdk5s.
Cancer

Ref: Alberts et al, *Mol. Biol. Cell, 5e, Chapter 20*
Outline

• Overview

• Preventable causes of cancer

• Genetic basis of cancer

• Cancer treatment

• Current status
Overview

- Cancer is the second leading cause of death.
  ~11.4 million survivors in US (2006, NCI)

- Cancer has a unique importance to cell biology in helping us to understand regulation of cell behavior.

- Many basic discoveries in cell biology are closely associated with cancer research.
  - DNA repair
  - Cell signaling
  - Cell cycle
  - Apoptosis

Number of deaths for leading causes of death

- Heart disease: 616,067
- Cancer: 582,875
- Stroke (cerebrovascular disease): 155,952
- Chronic lower respiratory diseases: 127,924
- Accidents (unintentional injuries): 123,706
- Alzheimer’s disease: 74,632
- Diabetes: 71,382
- Influenza and Pneumonia: 52,717
- Nephritis, nephrotic syndrome, and nephrosis: 46,448
- Septicemia: 4,828

A Milestone in Cancer Research

• In 1979, Michael Bishop and Harold Varmus at UCSF discovered the first human oncogene c-Src.

• Their discovery opened a new era of cancer research in searching for the underlying molecular and cellular mechanisms.

• Research over the past three decades produced enormous amount of information about the molecular and cellular bases of cancer.
Some Basic Properties of Cancer Cells

• Cancer cells escape normal regulation mechanisms to proliferate at the expense of neighboring cells.

• Uncontrolled cell proliferation results in tumors.

• A tumor is considered a cancer only if it is malignant, i.e. its cells invade and colonize surrounding tissues.

• Cancer is a microenvironment process.
Different Origins of Cancer

- Cancers originate from specific tissues:
  - adenocarcinoma: glandular tissue
  - blastoma: embryonic tissue of organs
  - carcinoma: epithelial tissue
  - leukemia: blood cells
  - lymphoma: lymphatic tissue
  - myeloma: bone marrow
  - sarcoma: connective tissue (bone, cartilage, muscle)

- Epithelium is the sheet of cells that cover the inner or outer surface of a structure.

- ~80% of human cancers are carcinomas.
Chronic Myelogenous Leukemia (II)

- Philadelphia chromosome (1960)

- Reciprocal translocations of chromosome 9 & 22


- Bcr-Abl functions as a constitutively active tyrosine kinase (1984)

- Bcr-Abl actives many pathways related to cell proliferation

Weinberg, R. A. Biology of Cancer, 2007
Cancers From a Single Abnormal Cell

- Metastatic cancer cells can be traced to a primary tumor.
- Tumors often can be traced to a single abnormal cell.
- By the time of detection, many human cancers have been developing for years.
Development of Cancer (I)

- Genetic mutations occur naturally.
  - Mutation rate: 1 out of $10^6$ cell divisions
  - $10^{16}$ cell divisions $\rightarrow 10^{10}$ mutations

- Cancer development requires multiple mutations that accumulate over time.

- Genetic changes $\rightarrow$ changes in DNA
  Epigenetic changes $\rightarrow$ changes in gene expression

- Cancer cells emerge as "winners" of natural selection.
Development of Cancer (II)

- Epigenetic changes are inheritable and play important roles in cancer development.

- Two main types of epigenetic changes
  - Modifications of chromatin structure
  - Changes in DNA methylation
Development of Cancer (III)

- Initial development of cancer is gradual.

- Abnormal cells gradually accumulate more mutations or epigenetic changes during initial development.

- Cancer growth depends on defective control of cell division, cell differentiation, and apoptosis.
Development of Cancer (IV)

• Certain cancers may take decades to develop before symptoms become detectable.

• This offers the possibility of early detection and intervention.
Cancer Cells Are Genetically Unstable

- Human cancer cells accumulate genetic changes at much higher rates than normal cells.
  - Defective DNA damage checkpoints
  - Defective DNA repair mechanisms
  - Chromosome abnormalities
  - Epigenetic changes

- Cancer development relies on an optimized level of genetic instability.
Cancer Stem Cells (I)

• Like normal tissues, many cancers are organized in a hierarchical way.

• A small population of cancer stem cells is capable of infinite renewal and is responsible for maintaining the cell population of a tumor.

• Most tumor cells have limited capacity of self-renewal.
  - There is a very small chance (~1%) that a random chosen cell from a tumor will generate a tumor.
Cancer Stem Cells (II)

- Cancer stem cells likely result from epigenetic changes.

- There are strong evidences that some tumors evolve from abnormal tissue stem cells.
  - Only tissue stem cells stay long enough to accumulate mutations required for a cancer.

- Another possible source of cancer stem cells is through changes of a proliferating cell.
Metastasis

- Metastasis is responsible for 90% of cancer-related patient deaths.

- Metastatic cancers can no longer be contained by surgery or irradiation.

- Metastatic cancer cells must be able to survive and proliferate in new environments, a rare process called colonization.

- Could the metastatic cells be cancer stem cells?
Angiogenesis

• Tumors recruit blood supply for its survival and growth by secreting angiogenic signals.

Judah Folkman
http://www.childrenshospital.org/cfapps/research/data_admin/Site105/mainpageS105P0.html

• Secreted signals attract endothelial cells and stimulate growth of new blood vessels.

• Induced vessels are irregular and leaky.

• Induced vessels are potential targets for cancer therapy.
Microenvironment in Cancer Development

- Microenvironment of cancer plays a critical role in determining its development.

  Mina Bissell
  http://www.lbl.gov/LBL-Programs/lifesciences/BissellLab/main.html

- Supportive tissues (stroma) of cancer actively collaborate with cancer cells.

- Composition of the stroma
  - fibroblast
  - myofibroblast
  - inflammatory white blood cells
  - endothelial cells of blood and lymphatic vessels

- Cancer cells and stromal cells evolve together.
Six Hallmarks of Cancer

- Self-sufficiency in growth signals
- Insensitivity to anti-growth signals
- Evading apoptosis
- Limitless replicative potentials
- Sustained angiogenesis
- Tissue invasion & metastasis

Hanahan & Weinberg,
The hallmarks of cancer, Cell, 100:57, 2000.
Preventable Causes of Cancer
Environmental and Lifestyle Factors

- Mutations can not be completely avoided due to limitations of the accuracy of DNA replication and repair.
- Environmental and lifestyle factors play an important role in cancer development.
- Different cancers have different risk factors.

<table>
<thead>
<tr>
<th>environmental and lifestyle factors</th>
<th>cancer</th>
<th>% total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>occupational exposure</td>
<td>various types</td>
<td>1-2</td>
</tr>
<tr>
<td>tobacco related</td>
<td>lung, kidney, bladder</td>
<td>24</td>
</tr>
<tr>
<td>diet: low in vegetables, high salt, high nitrate</td>
<td>stomach, esophagus</td>
<td>5</td>
</tr>
<tr>
<td>diet: high fat, low fiber, fried and broiled foods</td>
<td>bowel, pancreas, prostate, breast</td>
<td>37</td>
</tr>
<tr>
<td>tobacco and alcohol</td>
<td>mouth, throat</td>
<td>2</td>
</tr>
</tbody>
</table>
Carcinogens, Viruses, & Infections

- Many cancer-causing factors induce mutations and DNA damages.

- Viruses and other infections play important roles in cancer development.

Table 20-1 Viruses Associated with Human Cancers

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>ASSOCIATED CANCER</th>
<th>AREAS OF HIGH INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA viruses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papovavirus family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warts (benign) carcinoma of the uterine cervix</td>
<td>worldwide worldwide</td>
<td></td>
</tr>
<tr>
<td>Hepatitis-B virus</td>
<td>Hepatocellular carcinoma</td>
<td>Southeast Asia, tropical Africa worldwide</td>
</tr>
<tr>
<td>Hepatitis-C virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpesvirus family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Burkitt’s lymphoma (cancer of B lymphocytes) nasopharyngeal carcinoma</td>
<td>West Africa, Papua New Guinea Southern China, Greenland</td>
</tr>
<tr>
<td>RNA viruses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrovirus family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human T-cell leukemia virus type I (HTLV-1)</td>
<td>adult T-cell leukemia/lymphoma</td>
<td>Japan, West Indies</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV, the AIDS virus)</td>
<td>Kaposi’s sarcoma</td>
<td>Central and Southern Africa</td>
</tr>
</tbody>
</table>

For all these viruses, the number of people infected is much larger than the numbers who develop cancer; the viruses must act in conjunction with other factors. Moreover, some of the viruses contribute to cancer only indirectly. HIV, for example, destroys helper T lymphocytes, which allows a herpes virus to transform endothelial cells. Similarly, hepatitis-C virus causes chronic hepatitis, which promotes the development of liver cancer.
Genetic Basis of Cancer
Two classes of cancer-critical genes
- Proto-oncogenes
- Tumor suppressor genes

Mutants of proto-oncogenes are called oncogenes.

Mutations of oncogenes and tumor suppressor genes can have similar effects.
Oncogenes & Tumor Suppressors (II)

- Oncogenes can be activated in many ways.
- Tumor suppressor genes can be lost in many ways.
Cancer Treatment
Traditional Cancer Therapy

- Traditional anticancer therapy draws on the weakened capabilities of cancer cell to survive DNA damages.

- Problems
  - Less specific to cancer stem cells
  - Drug resistance
  - Induced resistance to apoptosis
  - Other side effects
Rational Treatment of Cancer (I)

- More specific strategies based on genetic instability of cancer cells.

- More specific delivery of anticancer drugs using monoclonal antibodies.

- Development of specific small molecules.
Rational Treatment of Cancer (II)

- Cancer treatment by targeting angiogenesis.
- Cancer treatment by inducing immune responses.
- Cocktail approaches to suppress drug resistance.
- Genomic profiling makes specific treatment strategies possible.
- No magic solution. Still a long way to go…
Current Status
Current Status (I)

- The rate of cancer incidence starts to decline since the early 1990s.

- However, incidence rates of certain types of cancer are rising, e.g.
  - liver, pancreas, kidney cancer
  - leukemia
  - childhood cancers
  - brain cancers

Cancer trends progress report, NCI, 2007
Current Status (II)

- Death rates of common cancers are declining.
- Overall death rates are declining.
- Declining of death rates is slow.

Cancer trends progress report, NCI, 2007
Variations Among Different Ethnic Groups

Cancer trends progress report, NCI, 2007
Questions?
Supplementary Reading


