How do mutations cause cancer?
Cell Signaling Pathways

- Take information from outside of the cell and transmit the signal to create an output
- Examples: Cell division, cell death, responses to stress, etc.
Ras pathway – cell growth

Growth signal

Normal Cell

Ras

B-Raf

Mek

Activated growth genes

Cell growth and proliferation
Ras pathway – cell growth

Growth signal

Cancer Cell

Ras

B-Raf

Mek

Activated growth genes

Abnormal cell growth and division
There are many diverse types of cancer

- Depending on mutation, different signaling pathways are affected

Signaling Pathway A

Signaling Pathway B

Signaling Pathway C
Summary

• Properties of cancer cells
  – Abnormal growth and migration through the body

• Mutations in DNA and signaling pathways can cause cancer
  – Example: mutation in the Ras pathway that controls cell growth

• Cancer is not one disease!
Part 2: Cancer Therapies, Present and Future

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Leah Liu
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Objectives

• Learn about cancer therapies that attack **general** features common to all cancers

• Learn about cancer therapies that attack **specific** features or mutations found in individual cancers

• The **therapeutic window** is the medicine dosage range that is both effective AND safe
## Properties of Normal Cells vs. Cancer Cells

<table>
<thead>
<tr>
<th>Normal Cells</th>
<th>Cancer Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled growth</td>
<td>Uncontrolled growth</td>
</tr>
<tr>
<td>Stay within their home tissue</td>
<td>Can move to other tissues in the body</td>
</tr>
<tr>
<td>Maintain normal tissue structure</td>
<td>Disrupt tissue structure and cause</td>
</tr>
<tr>
<td></td>
<td>blood vessel growth</td>
</tr>
</tbody>
</table>
DNA replication during cell division

Dividing cell

DNA
General and Specific Features of Cancer Cells

Uncontrolled cell division and DNA replication

DNA mutation

AGCGTATGTGTCAC

AGCGTATCTGTCAC
Chemotherapy consists of chemicals that kill cells that divide rapidly.

Chemotherapy agents bind to DNA. Cell division is blocked, leading to cell death and tumor shrinkage. Most cells in the body do not divide frequently.
Therapeutic Window:

- Medicine dosages that are both safe and effective
Therapeutic Window:

Therapeutic window

Benefit

Dose

100 200
Chemotherapy causes side effects

- Inflammation of the digestive tract, nausea, diarrhea
- Hair loss
- Fewer blood cells, suppressed immune system (bone marrow)

Chemotherapy has a small therapeutic window

Why are the bone marrow, hair, and digestive tract affected?

• Chemotherapy attacks ANY fast-dividing cells, including but not limited to cancer cells

Blood cells in bone marrow

Hair follicle

Intestinal cells
How effective is chemotherapy?

• The 5 year survival rate for all cancers is 63%

• What would be the 5 year survival rate without chemotherapy?

A. 2%
B. 33%
C. 61%

$63\% - 61\% = 2\%$ of survival rate can be attributed to chemotherapy

Each type of cancer responds very differently to chemotherapy.

Adapted from Morgan, G., et al. Clinical Oncology (2004) 16:
Radiation therapy damages DNA.

Radiation is targeted to a specific body part. DNA Damage.

Cancer cells are bad at repairing DNA. Cell death, tumor shrinkage.

Normal cells can also be affected.

http://www.cancer.gov/cancertopics/factsheet/Therapy/radiation
Radiation Therapy causes side effects

- Fatigue, memory loss
- Skin irritation, scar tissue
- Chronic bowel effects
- Radiation therapy has a small therapeutic window
- Very rare secondary tumors

Different cancers respond very differently to radiation therapy

<table>
<thead>
<tr>
<th>Responsive Cancers</th>
<th>Resistant Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>Glioma</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Large bowel cancer</td>
</tr>
</tbody>
</table>
Summary: Current Cancer Therapies

• Chemotherapy attacks cells that divide rapidly such as cancer cells but other tissues too
• Radiation therapy damages DNA in cancer cells such that it cannot be repaired
• Both chemotherapy and radiation therapy have small therapeutic windows
General and Specific Features of Cancer Cells

Uncontrolled cell division and DNA replication

DNA mutation

AGCGTATGTGTCAC
AGCGTATCTGTCAC
There are many diverse types of cancer

- Depending on mutation, different signaling pathways are affected

Signaling Pathway A

Signaling Pathway B

Signaling Pathway C
“Targeted therapies” are medicines that interfere with specific mutated proteins necessary for tumor growth.

**Normal sequence**: AGCGTATGTGTCAC

**Mutated sequence**: AGCGTATCTGTCAC
“Targeted therapies” are medicines that interfere with specific mutated proteins necessary for tumor growth.

Functional protein

Oncogenic protein blocked

AGCGTATGTGTCAC
Normal sequence

AGCGTATCTGTCAC
Mutated sequence
Targeted therapies only work for patients with the correct mutation

• Patients must be tested for the targeted mutation before treatment
Targeted Therapies have fewer side effects

Joint pain, fatigue, skin lesions, for PLX4032

“minimal” side effects: nausea, muscle pain, diarrhea with Gleevec

Targeted therapies specifically target cancer cells which have the mutations and not normal cells and have a wider therapeutic window

Chronic myelogenous leukemia (CML) is a cancer of white blood cells.

Oncogenic BCR-ABL turns on cell division proteins in signaling pathway.

Uncontrolled cell division.
Chronic myelogenous leukemia is a cancer of white blood cells

Gleevec/imatinib

Oncogenic *BCR-ABL* Signaling pathways blocked

Uncontrolled cell division is stabilized

- CML currently has 89% 5-year survival rate compared to 23% in 1975
- Gleevec can be used for other cancers that have *BCR-ABL*

BRAF inhibitors for melanoma

- Melanoma, a type of skin cancer, is resistant to chemotherapy and radiation
- 68,000 new cases and 8,700 deaths/year in U.S.
- 40-60% of melanomas have a driver oncogene called \textit{BRAF}

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Over-activate signaling pathways for cell division

PLX4032/vemurafenib inhibits oncogenic BRAF

**Oncogenic B-Raf**

**Prevention of overactive cell division**

**Tumors shrink**
Examples of PLX4032 effectiveness during clinical trials

PLX4032 randomized clinical trial

336 patients with BRAF oncogene on PLX4032 → 63% less risk of death

6 months

336 patients with BRAF oncogene on chemotherapy → Chemotherapy group given opportunity to try PLX4032

Chapman, et al. NEJM 2011
Summary: Cancer Therapies

- Chemotherapy and radiation therapy attack general features of cancer cells
  - effective treatment for many, but not all types of cancer, and lead to side effects due to small therapeutic window
- Targeted therapies attack specific features (mutations) of cancer cells
  - Cancers with those mutations respond very well with fewer side effects
- Understanding the genetics of cancer is important for developing therapies