Genes Gone Wild
The Biology of Human Cancer

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Roadmap for the talk

1. Introduction to the biology of cancer

2. Cancer in the clinic
1. Introduction to the Biology of Cancer
Cancer impacts nearly all of our lives

1,658,370 estimated new cases in 2015

589,430 estimated deaths in 2015
Cancer is the second leading cause of death in the US

Leading Causes of Death in the US in 2013

- Heart Disease
- Cancer
- Lower Respiratory Disease
- Accidents
- Stroke
- Alzheimer's Disease
- Diabetes

What is cancer?

- Cancer is characterized by the **uncontrolled growth** of **abnormal** cells.

- Cancer is not a single disease but rather a term that refers to a collection of **many** diseases.

Cancer and tumor are not synonymous

**Tumor:** a mass of tissue lacking normal function

**Benign:** localized and does not spread to other parts of the body (cannot metastasize)

**Malignant:** invades nearby tissues and spreads to other parts of the body (can metastasize)

Cancer!
Cancer cells are different from normal cells

**Normal Cells**
- Grow and divide in an orderly fashion
- Die when they become old or damaged
- Carry out specialized functions
- Stick together in the right place in the body

**Cancer Cells**
- Grow and divide uncontrollably
- Resist death and continue to grow
- Lose ability to carry out specialized functions
- Invade other tissues
Cancer cells are different from normal cells

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Questions?
What causes cancer?

Accumulation of **genetic mutations** → Changes in production or activity level of **proteins**

![Diagram showing the cycle of genetic mutations leading to changes in protein activity, resulting in cancer.](image-url)
Cancer is a genetic disease

- **Acquired** mutations are the result of damages to the DNA of a cell accrued over a person’s life and are not heritable.

1) Environmental factors

- **Chemical carcinogens**
- **Radiation**

Cancer is a genetic disease

2) Errors in DNA replication

~3 billion base pairs of DNA in the cell

~1 mutation per 10 billion base pairs that are replicated
Cancer is a genetic disease

- **Acquired** mutations: damages to the DNA of a cell accrued over a person’s life and are not heritable
  1) Environmental factors
  2) Errors in DNA replication

- **Inherited** mutations: mutations present in your parents that you receive in every cell of your body
What kind of mutations are associated with cancers?

We have ~20,000 protein coding genes in our DNA. Mutations in most of these genes will not cause cancer.

Cancer is caused by mutations in two classes of genes: oncogenes and tumor suppressor genes.
Analogy: cells must control their growth like cars control their speed

**Oncogenes** drive cancer when inappropriately turned on like how a **stuck gas pedal** accelerates a car.

**Tumor suppressor genes** drive cancer when inappropriately turned off like how a **broken brake pedal** cannot slow down a car.
Oncogenes and tumor suppressors in normal cells and cancer cells

**Normal Cells**
- Genes which help cells grow appropriately by being turned on at the right time
- Genes which help
  1) prevent growth
  2) repair DNA damage

**Cancer Cells**
- Mutations cause the gene to be permanently turned on or activated
- Mutations cause the gene to be permanently turned off or inactivated
Oncogene
Ras: transmits the signal to grow

Signal $\rightarrow$ Growth

Growth Always On
Tumor Suppressor
BRCA: helps repair DNA damage

Mutated BRCA

Risk of breast cancer (%)

Breast cancer by age 50
Up to 50%
2%

Breast cancer by age 70
Up to 87%
8%

Ovarian cancer by age 70
Up to 44%
<1%

Questions?
Is a single mutation enough to develop cancer?

- It generally takes more than one mutation for cancer to develop.
- Cancer causing mutations build upon one another.

Individuals with inherited genetic mutations are more susceptible to developing cancer

First Mutation: Cell seems normal but is susceptible to developing cancer

Second Mutation: Cell acquires additional mutations and become less normal

Third Mutation: Cells grow faster and look more abnormal

Fourth Mutation: Cells grow uncontrollably and look very abnormal

Researchers are using cancer genome sequencing to understand cancer

• Some Goals
  – Identify driver mutations
  – Weed out passenger mutations
  – Advance personal medicine

• Findings
  – Certain genes are recurrently mutated in particular cancers
  – Analysis of 4,742 samples from 21 tumor types yielded 33 new genes
  – We still have more genes to find!

• Significance: huge number of potential new targets for cancer research and therapy

http://www.genome.gov/Course2014/
Summary

- Cancer is a collection of diseases that are characterized by uncontrolled growth of abnormal cells
- Cancer is a genetic disease caused by acquired or inherited mutations
- Mutations that cause cancer occur in oncogenes and tumor suppressor genes
- Typically more than one mutation is necessary before cancer develops, and each cancer is unique
- Cancer genome sequencing is identifying large numbers of potential new targets for cancer research and therapy

Questions?
2. Cancer in the Clinic

Disclaimer: All information provided here is for educational purposes only. I am not a medical doctor and I am in no way providing medical advice. While I hope that this information may be helpful to any patients or family members of patients, please discuss all medical decisions with a physician.
How does cancer harm the body?

**Tumor:** a mass of tissue lacking normal function

Tumors, whether benign or malignant, cause **disease** by interfering with normal function of neighboring tissues.

Malignant tumors can **metastasize**, or spread to other parts of the body, causing more disease and making treatment more difficult.
Melanoma is a very dangerous skin cancer

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Metastasis is a difficult, rare process
Metastasis Detection


Number of Divisions

20  25  30
Cancer Staging

- Staging is the categorization of cancers by severity
- Staging guides treatment, prognosis, clinical trials, and research

Considerations include:
- Tumor Size
- Regional Lymph Node Involvement
- Presence of Distant Metastasis
Cancer Staging

- Staging is the categorization of cancers by severity
- Staging guides treatment, prognosis, clinical trials, and research

Considerations include:
- Tumor Size
- Regional Lymph Node Involvement
- Presence of Distant Metastasis

- Different cancers often have their own staging systems (usually I to IV)
Melanoma Stage is Highly Predictive of Survival Probability
Summary (Part 1)

- Tumors cause disease by interfering with neighboring, normal tissues
- Malignant tumors can metastasize
- Just because a tumor can metastasize doesn’t mean it already has
- Staging allows us to categorize cancers by severity
- Presence of metastases defines highest stages

Questions?
Surgery is Very Effective for Localized Tumors

- Where is the tumor?
- How big is the tumor?
- Can we remove appropriate margins?
  - **Margins**: surrounding tissue removed with a tumor
- Ideally, remove all cancerous cells
Radiation Therapy - Local Treatment, Less Invasive

- But wait! I thought radiation caused cancer?
Chemotherapy- Treatment for the Whole Body

- Drugs that target rapidly dividing cells
  - Prevent cells from copying DNA
  - Inhibit cell division
- Side effects: lose normal, rapidly dividing cells

Joy Jiao
Resistance to Chemotherapy

- Tumors are made up of a diverse group of cells
- Cancerous cells are always gaining more mutations
- Chemotherapy can actually cause more mutations
- Only need one cell to mutate to survive therapy

1 in 1,000,000 → 1 in 1,000,000,000,000,000

Melanoma Treatment Differs by Stage, but is Usually Aggressive

![Graph showing survival probability over years for different stages of melanoma: Stage I (Surgery), Stage II (Surgery + Radiation), Stage III (Surgery, Radiation), and Stage IV (Surgery, Radiation, and Chemotherapy).](mmmp.org)
Targeted Therapies: the Future

- Chronic Myelogenous Leukemia (CML)
- Imatinib specifically inhibits BCR-ABL
Targeted Therapies are becoming easier to develop

- 1950
- 1960: Philadelphia Chromosome
- 1992: Imatinib Patent
- 2001: FDA Approval
- 2003: Human Genome
- 2006: 1st Cancer Genome
- 2015: >1,000 Cancer Genomes
BRAF Oncogene - 50% of Melanomas

Signal → Growth

Ras → BRAF → Signal → Growth

Sorafenib

Normal Ras → Mutated BRAF

Signal → Growth
Targeted Therapies are becoming easier to develop

1960: Philadelphia Chromosome

1992: Imatinib Patent

2000

2001: FDA Approval

2002: BRAF mutation

2007: Sorafenib FDA Approval

2011: Vemurafenib FDA Approval
## More Targeted Therapies are Rapidly Becoming Available

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cancer Type</th>
<th>Target</th>
<th>Year Approved</th>
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<tr>
<td>Tamoxifen (and related)</td>
<td>Breast</td>
<td>ER</td>
<td>1977</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Breast, Stomach</td>
<td>HER-2</td>
<td>1998</td>
</tr>
<tr>
<td>Imatinib (Gleevec)</td>
<td>CML, Stomach</td>
<td>BCR-ABL</td>
<td>2001</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Colon, Lung, Renal, Ovarian, Brain</td>
<td>VEGF-A</td>
<td>2004</td>
</tr>
<tr>
<td>Everolimus (Zortress)</td>
<td>Renal, Pancreatic, Breast</td>
<td>mTOR</td>
<td>2009</td>
</tr>
<tr>
<td>Vemurafenib (Zelboraf)</td>
<td>Melanoma</td>
<td>BRAF</td>
<td>2011</td>
</tr>
<tr>
<td>Vismodegib (Erivedge)</td>
<td>Skin</td>
<td>SMO</td>
<td>2012</td>
</tr>
<tr>
<td>Ramucirumab (Cyramza)</td>
<td>Stomach</td>
<td>VEGFR2</td>
<td>2014</td>
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Personalized Medicine

Tumor Biopsy

Blood

Sequencing and Analysis

Decide on most effective treatment

Inspire new targeted treatments

Adapted from S. Roychowdhury and A. Chinnaiyan, hhmi.org
Summary (Part 2)

• Surgery is effective at removing a single, localized tumor
• Radiation helps with localized tumors that we cannot surgically remove
• Traditional chemotherapies target rapidly dividing cells throughout the body
• Targeted therapies are being inspired by our rapidly increasing knowledge
Take Home Conclusions

• Cancer is a genetic disease caused by DNA mutations
• Cancer progression is tied to more mutations
• Metastasis is the spread of cancer to other tissues
• Surgery, radiation, and chemotherapies are our major current treatments
• Targeted therapies are becoming more numerous and allow us to attack the underlying causes of cancer

Questions?
Thank you!

SITN would like to acknowledge the following organizations for their generous support of this event.

Harvard Integrated Life Sciences

addgene
The nonprofit plasmid repository