When Good Cells go Bad

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Disclosure

- I have no actual or potential conflict of interest in relation to this program/presentation.
Cell Signaling

Loss of Tumor Suppressor Genes

Mutations
Gene Amplifications
Gene fusions
Environmental toxins
Carcinogens
Epigenetic events

Gain of Oncogenes

STOP!
Caution!
GO!
Roadmap for tonight...

• What is “cell signaling”?
• What are the major types of signals & signaling molecules?
• How do cells interpret signals?
• How do good cells go bad?

How do normal cells become cancer cells?
Form = Function...

- How does genetic information become functional?
- Mutations in DNA “encode” dysfunctional proteins...
  - Loss of function (no protein detected or inactivated)
  - Gain of function (too much protein or hyperactivated)

**Code:** Set of instructions

```
Form → mRNA → protein → Function
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Masonic Cancer Center
University of Minnesota

Comprehensive Cancer Center designated by the National Cancer Institute
Protein networks that relay information from the outside of the cell to the inside for the purpose of gene regulation.
Cell signaling is a relay of information...
Passing the signal is very precise...
Signals are very rapid...
Cells sense many different signals...
Structure of a normal cell

Plasma membrane

Cytoplasm

Nucleus

Chromatin: (DNA + proteins)
Structure of a normal cell

Molecular signal

Relay “signaling”

Decision

Chromatin: (DNA + proteins)
Cells have 3 decisions to make…

STOP  STAY  GO
Cells can “choose” among three decisions...

Extracellular Signals (growth factors)

Receptor Activation

Signal Transduction

“outside”

“inside”
(cyttoplasm)

“nucleus”

CANCER
Growth
STAY

Cell Suicide
Signaling pathways in cancer cells....
Roadmap for tonight…

• What is “cell signaling”?
• What are the major types of signals & signaling molecules?
• How do cells interpret signals?
Molecular Signals

- Amino acids (the building blocks of proteins)
- Small proteins (peptides) – insulin, growth factors
- Hormones (estrogen, androgen, cortisol, Vitamin D)
- Small Ions (Calcium, Sodium, Potassium)
- Gases (Nitric Oxide)

Signals tell the cell what to do and when…
Signaling molecules (runners in the relay)

- Receptors
- G Proteins
- Protein Kinases
- Transcription Factors

Proteins that pass the signal...
Signaling vocabulary 101

- Binding (hormone “binds” receptor)
- Conformational Change (protein shape change)
- Protein-Protein interaction (an example of binding)
- Enzymes (proteins that induce fast reactions)
- Protein Kinases (a very specific enzyme & reaction)
- Activation (the “ON” shape: signal is passed rapidly)
- Upstream vs. Downstream
- Protein “expression”
Receptors… (Her family of related growth factor receptors)

- Growth factor ligand binds receptor
- Conformational (shape) change
Receptors dimerize... (pair with partners)

- Dimerization
- Activation (signal is ON)
Her2 is commonly increased in breast cancer....
The drug Herceptin blocks Her2 receptor dimerization...
Signaling molecules (runners in the relay)

- Receptors
- G Proteins
- Protein Kinases
- Transcription Factors

Proteins that pass the signal...
G Proteins:
All signaling pathways require a light switch …

Outside

Inside

G

GTPase

Guanosine diphosphate

Guanosine triphosphate

+ Pi

− GTPase

Guanosine diphosphate

Guanosine triphosphate
G Proteins

- Bind Guanine nucleotides (GDP and GTP)
- Over 50 family members (related proteins)
- Molecular switches (flip ON and OFF)
G Protein

Cellular Decisions

(upstream)

(downstream)

Transcription
- Cell survival
- Cell growth
- Cell cycle progression
- Cell migration
- Transcription

Endocytosis
- Cytoskeleton
- Cell migration
- Ca²⁺ signalling
- Endocytosis
All signaling pathways require a light switch ...
How do G-proteins get permanently activated (ON)?

Mutation in the Ras gene (DNA) results in a protein in the ON position FOREVER.
Ras mutations are prevalent in deadly cancers...
Targeting RAS in cancers…

G Protein

BLOCK essential interactions

(downstream)

Cellular Decisions
Signaling molecules (runners in the relay)

- Receptors
- G Proteins
- Protein Kinases
- Transcription Factors

Proteins that pass the signal...
Protein kinases

- Enzymes (proteins that speed up chemical reactions)
- Add phosphate to other proteins
Protein Kinase Chemistry 101

- Change shape
- Change activity (flip ON or OFF)
- Change location inside cell
- Change binding to partners
Proteins are chemically modified... (phosphorylation)

Inactive “OFF” shape

Tyr416 is phosphorylated

Active “ON” Shape
Protein kinase cascades relay the signal: The signal (baton) moves deeper into the cell…

Outside

Inside

drugs

Gleevec
There are 100s of Protein Kinases…
Signals are very rapid...
Protein kinase cascades relay the signal: The signal (baton) moves into the nucleus...
Aberrant Kinases in ER+ Luminal Breast Cancer:

- Src overexpression with EGFR family members (~70%)
- Increased levels of ERK1/2 MAP Kinases (~50%)
- PIK3CA gain of function mutations (~45% of luminal BCs)
- PIK3CA gene amplification (10%)
- Upregulation of cyclin D1 (29% of luminal A; 58% of luminal B)
- Gain of CDK4 (14% of luminal A; 25% of luminal B)

Estrogen Receptor (ER)  
CDK4/6 (cell cycle dependent protein kinase 4/6)
CDK4/6 kinase inhibitors show promise in clinical trials.

**PALOMA-1: Progression-Free Survival (PFS) with Palbociclib/Letrozole in the First-Line Setting**

<table>
<thead>
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<th>Palbo/letrozole (n = 84)</th>
<th>Letrozole (n = 81)</th>
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<tbody>
<tr>
<td>mPFS(^1)</td>
<td>20.2 mo</td>
<td>10.2 mo</td>
</tr>
<tr>
<td>HR = 0.488, (p = 0.0004)</td>
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<tr>
<td>mOS(^2)</td>
<td>37.5 mo</td>
<td>34.5 mo</td>
</tr>
<tr>
<td>HR = 0.897, (p = 0.281)</td>
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</tbody>
</table>

\(^2\) Finn RS et al. *Proc ASCO* 2017;Abstract 1001.
Signaling molecules (runners in the relay)

- Receptors
- G Proteins
- Protein Kinases
- Transcription Factors

Proteins that pass the signal...
Transcription Factors

Genes are regulated by proteins called “transcription factors” that interact directly with DNA to turn genes ON or OFF (to create a protein product or not).

Transcription factors are proteins that regulate epigenetic events on DNA.
Transcription factors contact (bind) DNA…

Four p53 proteins on DNA (turn ON genes)
Loss of function mutations in p53

Mutant p53 CANNOT BIND DNA

TP53 VAF
>40%

TP53 VAF
20%-40%

TP53 VAF
<20%

TP53 domains
- Transactivation
- Proline rich
- DNA binding
- Oligomerization
- Nuclear localization
How do elephants avoid cancer?

20 copies of TP53 gene (p53 protein)

Peto’s Paradox – why don’t larger organisms get more cancer?
Roadmap for tonight...

- What is “cell signaling”? 
- What are the major types of signals & signaling molecules? 
- How do cells interpret signals?
What is DNA?

- Biochemical information storage and retrieval system (a cell’s hard drive).
- Contains only 4 different components (A, C, G, and T) linked in two anti-parallel strands.

Section of DNA (like a computer file) that has information for a particular protein.
How do transcription factors know where to go?

**Genome:**

3.2 billion base pairs / cell
(6.4 billion bases / cell)
Dr. Lange’s Cabin!
Protein kinases 101

- Add phosphate to other proteins!!!
Phosphorylation = Mailing Address

- Eiffel Tower (gene 1)
- 221 B Baker St. (gene 2)
- Dr. Lange’s Cabin (gene 3)
Transcription factors are heavily phosphorylated...
The finish line of the signaling relay is DNA!
The address in your DNA is key...

Overlook Hotel...
Jack Torrance

Dr. Lange’s cabin...
You've come to the correct address!

Altered Cell Signaling = Misinformation

WRONG ADDRESS!
Roadmap for tonight...

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- How do good cells go bad?

Mutations in our DNA encode dysfunctional signaling proteins, leading to inappropriate cellular decisions.
Cancer is a cell signaling problem!
Cancer cells make inappropriate decisions!
What is "cell signaling"?

What are the major types of signals & signaling molecules?

How do cells interpret signals?

Hormones are highly specialized signals.

Many cancers are influenced by hormonal signals.

The Finish Line...
Thank you!
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