Cell cycle
what goes wrong in cancer?

Prof. Charlotte Moser

cancer

a malignant growth or tumor, uncontrolled cell division, growth or tumor.
Learning Objectives

- To see the cell in the context of tissue, organs and our body
- To understand the cell cycle as an “engine” or “clock”
- What provokes cancer
- To appreciate the central role of signaling proteins
- To appreciate cancer as a disease of impaired cell cycle exit
  and altered cellular differentiation
Staring with 1 cell getting a unique combination of millions of cells: a human body
The cell
stem cells

What is a stem cell?

A single cell that can

replicate itself, or...

differentiate into many cell types.

Cell multiplication

Skin
Blood
Bowel
Lung
Bladder
Prostate
Breast

in contrast to
Bone
Brain
Nerves
Heart
Vessels
Liver
Kidney
Risk of errors in DNA replication

The body is always copying DNA and making new cells.
DNA repair
Repair not always sufficient
Cancer is a genetic disease

CAUSES OF CANCER

Cancer starts with a mutation in the DNA.

**Mutation** – A change to the DNA sequence.

*Not all mutations are harmful.* Some mutations do not affect an organism, while some cause health problems like cancer.
Cell control

Loss of Normal Growth Control

- Normal Cell Division
  - Cell Suicide or Apoptosis
  - Cell Damage—No Repair

- Cancer Cell Division
  - First Mutation
  - Second Mutation
  - Third Mutation
  - Fourth or Later Mutation
  - Uncontrolled Growth

Adapted from the National Cancer Institute
uncontrolled cell growth
Cell damage

DNA Damage

Cellular Metabolism, UV Light Exposure, Ionizing Radiation, Chemical Exposure, Replication Errors

DNA Repair:
- Direct reversal
- Base excision repair
- Nucleotide excision repair
- Mismatch repair
- Double strand break repair
  - Homologous recombination
  - Non-homologous end joining

Apoptosis

Cell Cycle Checkpoint Activation, Transcriptional Program Activation

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Smoking is the leading cause of cancer and death.
### Key causes of cancer

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>65.5</td>
</tr>
<tr>
<td>Alcohol</td>
<td>46.1</td>
</tr>
<tr>
<td>Lack of fruit &amp; vegetables</td>
<td>21.7</td>
</tr>
<tr>
<td>Meat</td>
<td>20.6</td>
</tr>
<tr>
<td>Lack of fibre</td>
<td>2.7</td>
</tr>
<tr>
<td>Overweight</td>
<td>2.6</td>
</tr>
</tbody>
</table>

#### Cancer causes by type:

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus (gullet)</td>
<td>65.5</td>
</tr>
<tr>
<td>Colorectal (bowel)</td>
<td>21.1</td>
</tr>
<tr>
<td>Breast</td>
<td>8.7</td>
</tr>
</tbody>
</table>

The most common cancers worldwide:

- **Women**:
  - Breast: 548,000
  - Lung: 677,000
  - Stomach: 653,000
  - Cervical: 140,000
  - Colorectal: 110,000
- **Men**:
  - Lung: 866,000
  - Breast: 645,000
  - Stomach: 675,000
  - Prostate: 620,000
  - Colon: 540,000

Cancers that caused the most deaths in 2007:

- Lung: 1,4m
- Stomach: 866,000
- Colon: 677,000
- Liver: 653,000
- Breast: 548,000
Normal cell → increasing numbers of genetic change → Cancer
All Cancer is Genetic, Not All Cancer is Inherited

Sporadic Cancer
- Normal cell
- First mutation
- Second mutation
- Third mutation
- Fourth + mutation
- Malignant cell

Hereditary Cancer
- First mutation
- Second mutation
- Third mutation
- Malignant cell

Examples of Dominantly Inherited Cancer Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Associated Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial retinoblastoma</td>
<td>RB1</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>TP53 (p53 protein)</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
<td>MLH1, MSH2, MSH6 PMS1, PMS2</td>
</tr>
<tr>
<td>Wilms’ tumor</td>
<td>WT1</td>
</tr>
<tr>
<td>Breast and ovarian cancer</td>
<td>BRCA1, BRCA2</td>
</tr>
<tr>
<td>von Hippel-Lindau</td>
<td>VHL</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
</tr>
</tbody>
</table>
Multiple mutations
Cancer growth

Uncontrolled growth
Invasion in surrounding tissue
Capacity to migrate
Cancer growth

Creation of own blood supply
Creation of own sugar supply
Preventing tumor growth

Apoptosis

Immune evasion
- Hypoxia
- Inflammation
- Angiogenic switch
- Macrophage polarization switch (reversible?)

Immune suppression
- Inhibition of cytolytic granule release
- M1 phenotype blocked
- Tumor-associated Ag presentation inhibited

Angiogenesis
- TGF-β, MCP1, PDGF, FGF, proteases
- EMT(?)
- EGF
- VEGF
- VEGF-C
- VEGF-D
- EndMT(?)

Influences by TAMs
- MMPs
- Cathepsins

Influences by CAFs
- Anti-tumorigenic macrophage
- Pro-tumorigenic TAM
- Normal fibroblasts
- CAFs
- T cell
- B cell
- NK cell
- Dendritic cell
- Tumor cell

MSC

CSF1

EndMT(?)
Different changes
How to escape check points
Cell cycle is a "clock" driven by the enzymatic activity of cell cycle phase-specific cyclins and cyclin-dependent kinases.
The tumor suppressor proteins form a network of checkpoints that prevent uncontrolled growth.
Tumor-suppressor genes inhibit cell division.

Proto-oncogenes stimulate cell division.
A tumor suppressor gene, or anti-oncogene, is a gene that protects a cell from one step on the path to cancer. When this gene mutates to cause a loss or reduction in its function, the cell can progress to cancer, usually in combination with other genetic changes.

**P53, Rb, p16, BRCA**
Proto-oncogenes are genes that normally help cells grow. When it mutates (changes), it becomes a "bad" gene that can become permanently turned on and the cell grows out of control, which can lead to cancer.

Cyclin D, HER2, Myc, RAS, BCL
Drugs?
The genetic progression of pancreatic carcinoma
Action of chemotherapy drugs

- Cell cycle dependent
- Cell cycle independent

NO activity in G1

**FIGURE 1.** Phases of the cell cycle with examples of anticancer drugs showing selective or preferential cell-cycle cytotoxicity.
Evolution: Why Chemotherapy Fails

1. Therapy
2. Resistant sub-clone
3. Relapse

Akiyama & Nesse, 2013
More selective drugs
IMATINIB GREATLY IMPROVED SURVIVAL IN GIST

Results from the Conticanet series of GIST patients demonstrated the huge survival benefit conferred by the new therapy

Figure 1: The Penetrating Powers of Alpha, Beta, and Gamma Rays,
North Dakota Department of Health
Repair of Radiation Damage & Dose Rate Effect

How nucleotide excision repair protects against cancer  Errol C. Friedberg Nature Reviews Cancer 1, 22-33 (Oct 2001)
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  - Oncogenes
  - Tumor suppressors
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